Uniwersytet Jagielloński
Collegium Medicum
Wydział Nauk o Zdrowiu

Katarzyna Klaś

Etyczne aspekty stosowania akceleratorów metodologicznych i organizacyjnych w badaniach klinicznych

Praca doktorska

Promotor:
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Pracę wykonano w Zakładzie Bioetyki w Instytucie Pielęgniarstwa i Położnictwa Uniwersytetu Jagiellońskiego Collegium Medicum

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Podziękowania

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Spis treści

Streszczenie

Wstęp: Proces planowania i prowadzenia badań klinicznych zwykle jest bardzo czasochłonny i charakteryzuje go wysoki wskaźnik niepowodzeń. Jednak na przestrzeni ostatnich dwóch dekad badania kliniczne wyraźnie ewoluowały. Proponowane są nowe metody prowadzenia badań klinicznych, aby przyspieszyć opracowywanie i zatwierdzanie leków w przyszłości oraz zmniejszyć wskaźnik niepowodzeń w rozwoju nowych terapii. Zmiany jakie obserwujemy w obszarze badań klinicznych są także efektem nowych wyzwań, przed którymi staje środowisko badawcze. Pandemia COVID-19 doprowadziła do uruchomienia w krótkim czasie bardzo dużej liczby badań klinicznych. Przyspieszenie badań klinicznych i opracowanie nowych modeli badań klinicznych może być bardzo korzystne, ale może też generować i pogłębiać powszechne problemy w zakresie etyki badań i rzetelności badawczej.

Cel: Głównym celem prac badawczych była analiza wybranych aspektów etycznych badań klinicznych, w których zastosowano tzw. akceleratory metodologiczne i organizacyjne. Akceleratory metodologiczne i organizacyjne w kontekście niniejszej pracy doktorskiej odnoszą się do nowych rozwiązań w zakresie projektowania i metodologii badań klinicznych oraz usprawnień instytucjonalnych i regulacyjnych. Celem ich stosowania jest prowadzenie szybszych, bardziej zoptymalizowanych i skoncentrowanych na pacjencie badań klinicznych.

Metody: Rozprawa doktorska składa się z czterech publikacji: dwóch analiz empirycznych opartych na danych z rejestru badań klinicznych, jednego przeglądu systematycznego z metaanalizą oraz jednej normatywnej analizy etycznej. Prace badawcze podzielono na dwa etapy. W pierwszym etapie dokonano analizy wybranych aspektów etycznych badań klinicznych testujących metody leczenia i zapobiegania COVID-19. W drugim etapie dokonano analizy wybranych aspektów etycznych nowych modeli badań klinicznych w obszarze onkologii. Omawiane zagadnienia etyczne odnoszą się do nadrzędnych zasad etycznego prowadzenia badań klinicznych takich jak unikanie marnotrawstwa badawczego, wartość naukowa i społeczna czy zasada proporcjonalności ryzyka i korzyści.

Wyniki: Artykuł *„How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov”* to systematyczna analiza informatywności badań klinicznych testujących metody leczenia i zapobiegania chorobie COVID-19, które zostały zarejestrowane w rejestrze *ClinicalTrials.gov*. Informatywność w kontekście badań klinicznych określa, czy badanie jednoznacznie odpowie na postawione pytania badawcze

i czy wesprze podejmowanie decyzji klinicznych. Przeanalizowano 500 badań klinicznych. Wykazano, że zaledwie jedna trzecia badań uruchomionych w początkowym okresie pandemii COVID-19 spełniła kryteria w zakresie wysokiej jakości projektu badania, ważności testowanej hipotezy badawczej oraz wykonalności celów rekrutacyjnych i zaplanowanego czasu trwania badania. Oznacza to, że pomimo szybkiego rozpoczęcia, badania te miały małe szanse na dostarczenie wysokiej jakości dowodów naukowych, co przyczyniło się do marnotrawstwa badawczego.

Artykuł *„Ethical challenges of clinical trials with a repurposed drug in outbreaks”* to analiza normatywna wyzwań etycznych związanych z uruchomieniem badań klinicznych dla leków o zmienionym przeznaczeniu na przykładzie amantadyny w czasie pandemii COVID-19. Amantadyna w czasie pandemii COVID-19 wzbudziła ogromne zainteresowanie jako potencjalny środek leczniczy. Popularność leku stymulowała głośna publiczna debata. Pomimo braku dowodów na skuteczność i negatywnych rekomendacji środowisk naukowych, w Polsce była na szeroką skalę przepisywana pacjentom chorującym na COVID-19. W odpowiedzi na ogromne zainteresowanie lekiem, Agencja Badań Medycznych sfinansowała dwa badania kliniczne, których celem była ocena skuteczności amantadyny w leczeniu i zapobieganiu COVID-19. W artykule podjęto dyskusję czy zasadne było uruchomienie tych badań klinicznych. Analiza ta wskazuje, że presja społeczna i obawa przed dezinformacją mogą etycznie uzasadniać inicjowanie badań, nawet gdy podstawy naukowe są słabe. Za takim rozwiązaniem przemawia m.in. analiza kosztu społecznego, polegającego na masowym stosowaniu substancji (w tym przypadku amantadyny) o niepotwierdzonej skuteczności do wskazań niezgodnych z przeznaczeniem leku (w tym przypadku COVID-19).

Artykuł *„Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis”* to przegląd systematyczny z metanalizą na temat ryzyka i korzyści koszykowych badań klinicznych w onkologii. W odróżnieniu od tradycyjnych modeli badań klinicznych, które najczęściej pozwalają na ocenę pojedynczej interwencji w ramach jednego rodzaju nowotworu, badania koszykowe umożliwiają ocenę nowych metod leczenia w grupie uczestników z różnymi typami nowotworów (niezależnie od lokalizacji), które charakteryzują się obecnością określonego biomarkera lub zmiany molekularnej. Artykuł dostarcza danych na temat wskaźników odpowiedzi oraz odsetka uczestników, którzy doświadczyli ciężkich (w tym tych śmiertelnych) działań niepożądanych związanych z leczeniem. Wykazano, że skumulowany wskaźnik obiektywnych odpowiedzi na leczenie dla wszystkich 126 uwzględnionych badań wyniósł 18,0%. Mediana

przeżycia wolnego od progresji wyniosła 3,1 miesiąca, a mediana przeżycia całkowitego – 8,9 miesiąca. Całkowity wskaźnik zgonów związanych z leczeniem wyniósł 0,7%, a 30,4% uczestników badania doświadczyło działań niepożądanych związanych z leczeniem stopnia 3–4. Udowodniono, że trudno jednoznacznie odpowiedzieć, czy badania koszykowe są szansą dla uczestników w zakresie korzystniejszego profilu ryzyka i korzyści porównaniu do innych modeli badawczych.

Artykuł *„Seamless trials in oncology: A cross-sectional analysis of characteristics and reporting”* to analiza cech i raportowania badań klinicznych o modelu ciągłym stosowanych we wczesnej fazie rozwoju leków w onkologii, które zostały zarejestrowane w rejestrze *ClinicalTrials.gov*. Badania o modelu ciągłym umożliwiają płynne przejście między fazami rozwoju klinicznego. Przejrzyste, transparentne i pełne raportowanie metod i wyników wszystkich badań klinicznych jest uznane za etyczny i naukowy wymóg mający na celu promowanie kompletnej bazy dowodowej i ograniczenie marnotrawstwa badawczego. Do analizy włączono 1051 badań. Wykazano, że wyniki tych badań są w niskim stopniu raportowane w rejestrze *ClinicalTrials.gov* – wyniki zostały opublikowane dla 34,7% spośród analizowanych badań. Dodatkowo udowodniono, że należy podjąć wysiłki w celu dostosowania funkcjonalności bazy danych *ClinicalTrials.gov* do nowych modeli badań klinicznych. Istotne jest, aby dostępne tam dane były spójne i przedstawione w sposób przystępny, nawet jeśli model badania klinicznego jest złożony.

Wnioski: Cykl publikacji przedstawiony w niniejszej dysertacji pokazuje, że organizacyjne i metodologiczne formy akceleracji prowadzenia badań klinicznych powinny wiązać się ze ścisłym nadzorem i monitoringiem takich przedsięwzięć. Pozwoli to na ciągłe udoskonalanie rozwiązań i utrzymanie bezpieczeństwa uczestników na wysokim poziomie. Rozważając przyspieszenie badań klinicznych należy wziąć pod uwagę szereg kwestii organizacyjnych oraz zmian regulatorowych, które są konieczne do wprowadzenia zmian. Jednocześnie nie należy zapominać o kwestiach etycznych tych badań. Zasady etyczne chronią uczestników badań, a także mają zagwarantować wysoką jakość dostarczanych danych, przeciwdziałając tym samym marnotrawstwu badawczemu i narażeniu uczestników na niepotrzebne ryzyko.

Abstract

Introduction: Planning and conducting clinical trials is typically a lengthy and failure-prone process. Over the past two decades, however, significant progress has been made. Novel approaches to trial design and execution are being proposed to accelerate the development and approval of future drugs, as well as to reduce the failure rate in the development of new therapies. The changes we are observing in clinical trials are also the result of new challenges facing the research community; for example, the rapid launch of a large number of trials during the COVID-19 pandemic. While accelerating clinical trials and developing new models can be beneficial, it can also introduce or exacerbate longstanding concerns related to research ethics and integrity.

Aim: The main objective of this thesis was to analyse the ethical aspects of using methodological and organisational accelerators in clinical trials. In this context, methodological and organisational accelerators refer to new solutions in the design and methodology of clinical trials, as well as institutional and regulatory improvements. Their purpose is to enable faster, more optimised, patient-centred clinical trials.

Methods: The thesis consists of four publications: two empirical analyses based on clinical trial registry data, one systematic review with meta-analysis, and one normative ethical analysis. The research was conducted in two stages. The first stage involved analysing selected ethical aspects of clinical trials testing methods of treating and preventing diseases caused by the SARS-CoV-2 virus. The second stage involved analysing selected ethical aspects of new clinical research models in oncology. The ethical issues discussed relate to overarching principles of the ethical conduct of clinical trials, such as avoiding research waste and ensuring scientific and social value, as well as the principle of proportionality of risk and benefit.

Results: The article *'How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov'* provides a systematic analysis of the informativeness of 500 trials registered during the early phase of the COVID-19 pandemic. The included trials tested therapeutic and preventative methods against the disease caused by the SARS-CoV-2 virus. In clinical trials, informativeness refers to a trial's ability to clearly answer the research questions posed and support clinical decision-making. The analysis found that only one third of the studies launched in the early period of the pandemic met the criteria for informativeness: namely high-quality study design, the importance of the tested research hypothesis and the feasibility of the recruitment objectives and the planned study duration. Despite

their rapid initiation, these studies lacked the conditions necessary to provide high-quality scientific evidence, resulting in research waste.

The article *'Ethical challenges of clinical trials with a repurposed drug in outbreaks'* provides a normative analysis of the ethical issues surrounding the launch of clinical trials for repurposed drugs, using amantadine as a case study during the SARS-CoV-2 pandemic. Amantadine attracted significant attention as a potential therapeutic agent during the pandemic, driven largely by intense public debate. Despite the absence of efficacy data, and negative recommendations from the scientific community, it was widely prescribed to COVID-19 patients in Poland. In response, the Medical Research Agency financed two clinical trials to assess amantadine's effectiveness both treatment and prevention. The article discusses whether launching these trials was justified. The analysis suggests that social pressure and fear of misinformation could ethically justify the initiation of research, even when the scientific basis is weak. This position is supported by an analysis of the social cost associated with widespread use of an ineffective substance for purposes other than those for which it was originally intended (in this case, amantadine for the treatment of patients with SARS-CoV-2).

The article *'Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis'* is a systematic review with meta-analysis of the risks and benefits of basket trials in oncology. Unlike traditional clinical trial designs, which typically evaluate a single intervention for a single cancer type, basket trials evaluate new treatments across a range of participants with different cancer types (regardless of location) that are characterized by a specific biomarker or molecular alteration. The article provides data on response rates and the percentage of participants who experience severe (including fatal) treatment-related adverse events. The pooled objective response rate for all 126 included studies was 18.0%. The median progression-free survival was 3.1 months, and the median overall survival was 8.9 months. The overall treatment-related death rate was 0.7%, and 30.4% of patients experienced grade 3–4 treatment-related adverse events. It has been proven difficult to unequivocally answer whether basket trials offer participants a more favourable risk–benefit profile compared to other research models.

The article *'Seamless trials in oncology: A Cross-Sectional Analysis of Characteristics and Reporting'* is an analysis of the characteristics and reporting of seamless clinical trials used in the early stages of drug development for oncology registered with the *ClinicalTrials.gov* registry. Seamless trials facilitate a smooth transition between clinical development phases. Transparent and complete reporting of trial methods and results is considered an ethical and scientific

obligation, as it promotes comprehensive evidence base and reduces research waste. The analysis included 1,051 studies and revealed that reporting quality in the *ClinicalTrials.gov* registry was poor, with publication occurring for only 34.7% of the analysed studies. Additionally, the need to adapt the functionality of the *ClinicalTrials.gov* database to new clinical trial models was proven. It is important that all available data are presented in a consistent and accessible way, even if the clinical trial design is complex.

Conclusions: The series of publications presented in this dissertation demonstrate that the organisational and methodological acceleration of clinical trials should be accompanied by rigorous supervision and monitoring. This is necessary to enable continuous improvement of solutions while maintaining a high level of participant safety. Organizational changes and regulatory adjustments must be taken into account when considering the acceleration of clinical trials. At the same time, the ethical issues of these studies must not be overlooked. These principles not only protect research participants, but also uphold the integrity of the data provided, thus minimizing research waste and preventing participants from unnecessary exposure to risk.

1 Wykaz publikacji stanowiących rozprawę doktorską

Rozprawa doktorska została przygotowana na podstawie **czterech artykułów** opublikowanych w międzynarodowych czasopismach naukowych:

P1. Hutchinson N, **Klas K**, Carlisle BG, Kimmelman J, Waligora M. *How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov*. PLoS One. 2022 Jan 21;17(1):e0262114.
doi: 10.1371/journal.pone.0262114. [1]
Punktacja ministerialna: 100. Impact Factor: 3,7.

P2. **Klas K**, Strzebonska K, Waligora M. *Ethical challenges of clinical trials with a repurposed drug in outbreaks*. Med Health Care Philos. 2023 Jun;26(2):233-241.
doi: 10.1007/s11019-023-10140-4. Epub 2023 Mar 7. [2]
Punktacja ministerialna: 100. Impact Factor: 2,1.

P3. **Klas K**, Strzebonska K, Zaborowska L, Krawczyk T, Włodarczyk A, Bąk-Kuchejda U, Polak M, Van Wambeke S, Waligora M. *Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis.* Target Oncol. 2025 Jan;20(1):89-101.
doi: 10.1007/s11523-024-01107-3. Epub 2024 Oct 26. [3]
Punktacja ministerialna: 100. Impact Factor: 4,4.

P4. **Klas K**, Strzebonska K, Buedo P, Włodarczyk A, Gordon S, Kaszuba P, Polak M, Waligora M. *Seamless trials in oncology: A cross-sectional analysis of characteristics and reporting.* PLoS One. 2024 Dec 3;19(12):e0312797.
doi: 10.1371/journal.pone.0312797. [4]
Punktacja ministerialna: 100. Impact Factor: 2,9.

Suma punktów według wykazu czasopism naukowych Ministerstwa Nauki i Szkolnictwa Wyższego wynosi **400**. Łączna wartość wskaźnika *Impact Factor* wynosi **13,1**.

2 Źródła finansowania badań

Badania przedstawione w niniejszej rozprawie doktorskiej zostały sfinansowane ze środków następujących projektów badawczych:

- **Etyka badań klinicznych w czasie pandemii COVID-19**

Źródło finansowania: Narodowe Centrum Nauki, Szybka ścieżka dostępu do funduszy na badania nad COVID-19
Numer projektu: 2020/01/0/HS1/00024
Okres realizacji: 2020-2022
Kierownik projektu: dr hab. Marcin Waligóra, prof. UJ

- **Nowe modele prowadzenia badań klinicznych. Analiza ryzyka i korzyści**

Źródło finansowania: *Research Support Module*, Inicjatywa Doskonałości w Uniwersytecie Jagiellońskim (ID.UJ)
Numer projektu: U1C/W43/NO/28.04
Okres realizacji: 2022-2023
Kierownik projektu: mgr Katarzyna Klaś

- **Pacjent w centrum? Bioetyczne aspekty stosowania metod adaptacyjnych w badaniach klinicznych z udziałem ludzi**

Źródło finansowania: Narodowe Centrum Nauki, OPUS 21
Numer projektu: 2021/41/B/HS1/01123
Okres realizacji: 2022-2026
Kierownik projektu: dr hab. Marcin Waligóra, prof. UJ

3 Wykaz pozostałych publikacji Autorki związanych z realizacją Indywidualnego Planu Badawczego

1. Nilsonne G, Wieschowski S, DeVito NJ, Salholz-Hillel M, Ahnström L, Bruckner T, **Klas K**, Suljic T, Yerunkar S, Olsson N, Cruz C, Strzebonska K, Småbrekke L, Wasylewski MT, Bengtsson J, Ringsten M, Schuster A, Krawczyk T, Paraskevas T, Raittio E, Herczeg L, Hesselberg JO, Karlsson S, Borana R, Bruschettini M, Mulinari S, Lizárraga K, Siebert M, Hildebrand N, Ramakrishnan S, Janiaud P, Zavalis E, Franzen D, Boesen K, Hemkens LG, Naudet F, Possmark S, Willén RM, Ioannidis JPA, Strech D, Axfors C. Results reporting for clinical trials led by medical universities and university hospitals in the nordic countries was often missing or delayed. J Clin Epidemiol. 2025 Feb 1;181:111710. doi: 10.1016/j.jclinepi.2025.111710.

2. Buedo P, Bianchini A, **Klas K**, Waligora M. *Bioethics of somatic gene therapy: what do we know so far?* Curr Med Res Opin. 2023 Oct;39(10):1355-1365. doi: 10.1080/03007995.2023.2257600. Epub 2023 Oct 10.

3. Hutchinson N, **Klas K**, Carlisle BG, Polak M, Kimmelman J, Waligora M. *Competition for recruitment in SARS-CoV-2 Trials in the United States: a longitudinal cohort analysis*. BMC Res Notes. 2022 Dec 12;15(1):368. doi: 10.1186/s13104-022-06263-1.

4. Waligora M, **Klas K**. *Masking*. In The SAGE Encyclopedia of Research Design. Vol. 4. 2 ed. Thousand Oaks, CA: SAGE Publications, Inc.; 2022: 860-861. doi:10.4135/9781071812082

4 Osiągnięcia Autorki oraz wykaz aktywności związanych z realizacją Indywidualnego Planu Badawczego

Nagrody i stypendia

- Stypendium START Fundacji na rzecz Nauki Polskiej (nagroda w dziedzinie *nauki o zdrowiu*), 2025.
- Nagroda dla Najlepszego Doktoranta Szkoły Doktorskiej Nauk Medycznych i Nauk o Zdrowiu: Nagroda III stopnia za osiągniecia naukowo-organizacyjne, 2023.
- Nagroda dla Najlepszego Doktoranta Szkoły Doktorskiej Nauk Medycznych i Nauk o Zdrowiu: Nagroda I stopnia za osiągniecia naukowo-organizacyjne, 2022.
- Stypendium naukowe finansowane ze środków Narodowego Centrum Nauki w ramach projektu *Pacjent w centrum? Bioetyczne aspekty stosowania metod adaptacyjnych w badaniach klinicznych z udziałem ludzi* (OPUS 21, 2021/41/B/HS1/01123). Kierownik projektu: dr hab. Marcin Waligóra, prof. UJ.

Staż badawczy

- McGill University, Faculty of Medicine, Biomedical Ethics Unit, Studies of Translation, Ethics, and Medicine (STREAM) research group, Montreal (Kanada). Czas trwania stażu: 01-12.05.2023. Opiekun stażu: Prof. Jonathan Kimmelman.

Prezentacja wyników badań na konferencjach naukowych

- Global Evidence Summit 2024, Praga (Czechy), 10-13.09.2024, prezentacja posterowa.
- 36th European Conference on Philosophy of Medicine and Health Care “Medicine, healthcare, and the market”, Frankfurt/Offenbach (Niemcy), 21-24.08.2024, prezentacja ustna.
- International Dialogue on Bioethics, Health, and Research in Times of Disruptive Technologies, Kraków, 21-22.03.2024, prezentacja ustna.
- 35th European Conference on Philosophy of Medicine and Health Care “Methods in Bioethics and Philosophy of Medicine”, Ryga (Łotwa), 23-26.08.2023, prezentacja ustna.
- Oxford Global Health and Bioethics International Conference 2023, online, 26-27.06.2023, prezentacja posterowa.
- 16th World Congress of Bioethics 2022, Bazylea (Szwajcaria), 20-22.07.2022, prezentacja ustna.

- International Scientific Conference “Public Health – current achievements and new challenges”, online, 07-08.10.2021, prezentacja ustna.
- 1st Evidence-Based Research Conference: “Increasing the Value of Research”, online, 16-7.11.2020, prezentacja ustna.

Kursy i szkolenia (wybrane)

- Szkolenie *ICHE6 (R2) Good Clinical Practice*, Agencja Badań Medycznych, 2024.
- Studia podyplomowe *Badania kliniczne produktów leczniczych*, Medyczne Centrum Kształcenia Podyplomowego Collegium Medicum, Uniwersytet Jagielloński w Krakowie, 2023.
- Szkolenie *Etyczno-prawne aspekty badań klinicznych na ludziach*, Ośrodek ds. kształcenia podyplomowego na Wydziale Farmaceutycznym UJ CM w Krakowie, 2023.
- Szkolenie *Warsztaty z zakresu niekomercyjnych badań klinicznych dla farmaceutów*, Agencja Badań Medycznych, 2021.
- Szkolenie *Eksperyment medyczny a badanie kliniczne*, Agencja Badań Medycznych, 2021.
- Szkolenie *Podstawy badań klinicznych*, Grupa Szkoleniowa Polskiego Związku Pracodawców Firm Prowadzących Badania Kliniczne na Zlecenie (*Clinical Research Organizations*) – POLCRO, 2021.
- Szkolenie *VIRT2UE train-the-trainer program*, The Embassy of Good Science, 2021.
- Szkolenie *Introduction to the Principles and Practice of Clinical Research*, Office of Clinical Research, National Institutes of Health, 2021.
- Szkolenie *Ethical and Regulatory Aspects of Clinical Research Ethics*, Department of Bioethics, National Institutes of Health, 2020.

5 Wykaz skrótów

ABM	Agencja Badań Medycznych
ACT EU	ang. *Accelerating Clinical Trials in the EU*
CI	ang. *Confidence Interval*
	Przedział ufności
CIOMS	ang. *Council for International Organizations of Medical Sciences*
	Rada Międzynarodowych Organizacji Nauk Medycznych
EMA	ang. *European Medicines Agency*
	Europejska Agencja Leków
EU/UE	ang. *European Union*
	Unia Europejska
HMA	ang. *Heads of Medicines Agencies*
	Grupa Szefów Agencji Leków
ICH	ang. *International Council on Harmonisation*
	Międzynarodowa Rada Harmonizacji
ID.UJ	Inicjatywa Doskonałości - Uniwersytet Jagielloński
NIH	ang. *National Institute of Health*
	Narodowy Instytut Zdrowia
ORR	ang. *Objective Response Rate*
	Odsetek obiektywnych odpowiedzi
OS	ang. O*verall Survival*

	Przeżycie całkowite
PFS	ang. *Progression-Free Survival* Przeżycie wolne od progresji
POLCRO	Polski Związek Pracodawców Firm Prowadzących Badania Kliniczne na Zlecenie
PRISMA	ang. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*
STREAM	ang. *Studies of Translation, Ethics, and Medicine*
STROBE	ang. *Strengthening the Reporting of Observational Studies in Epidemiology*
REMEDY	ang. *Research Ethics in Medicine Study Group*
WHO	ang. *World Health Organization* Światowa Organizacja Zdrowia
ZNA	niderl. *Ziekenhuis Netwerk Antwerpen*

6 Omówienie pracy doktorskiej

6.1 Wstęp i uzasadnienie podjętej tematyki

Badania kliniczne są rodzajem badań naukowych prowadzonych z udziałem ludzi, podczas których ochotnicy otrzymują określone interwencje zgodnie z protokołem badawczym. Badania kliniczne odgrywają kluczową rolę w opracowywaniu nowych terapii. Umożliwiają ocenę bezpieczeństwa i skuteczności nowych leków i nowych metod leczenia. Badania kliniczne stanowią podstawę do zapewnienia obiektywnych i opartych na dowodach odpowiedzi na pytania w zakresie doboru postępowania terapeutycznego. Są siłą napędową generowania dowodów w medycynie i naukach o zdrowiu. Aby w pełni wykorzystać potencjał badań klinicznych, muszą one być etyczne, zapewniać bezpieczeństwo i ochronę uczestników badań, dostarczać wiarygodnych informacji oraz odpowiadać na ważne z naukowego punktu widzenia pytania badawcze [5, 6].

Proces planowania i prowadzenia badań klinicznych zwykle jest bardzo czasochłonny i charakteryzuje go wysoki wskaźnik niepowodzeń. Jednak na przestrzeni ostatnich dwóch dekad badania kliniczne wyraźnie ewoluowały [7]. Proponowane są nowe metody prowadzenia badań klinicznych, aby przyspieszyć opracowywanie i zatwierdzanie leków w przyszłości oraz zmniejszyć wskaźnik niepowodzeń w rozwoju nowych terapii [8-10]. Dzięki wsparciu organizacji regulatorowych, prowadzone są działania, aby badania kliniczne uczynić bardziej elastycznymi, wydajnymi i skoncentrowanymi na pacjencie [11]. Przykładem jest inicjatywa *Accelerating Clinical Trials in the EU* (ACT EU), która została uruchomiona w styczniu 2022 r. przez Komisję Europejską, Europejską Agencję Leków (EMA) i Grupę Szefów Agencji Leków (HMA) [12]. Celem ACT EU jest wdrożenie rekomendacji dotyczących innowacji w badaniach klinicznych, przekształcenie sposobu, w jaki badania kliniczne są projektowane, inicjowane i prowadzone, aby promować rozwój wysokiej jakości, bezpiecznych i skutecznych leków oraz lepiej integrować badania kliniczne w europejskim systemie opieki zdrowotnej [12].

Tradycyjnie badania kliniczne są przeprowadzane w serii kolejnych etapów. Na etapie przed rejestracją (tj. zanim badany produkt leczniczy zostanie dopuszczony do obrotu przez agencje regulatorowe) wyróżniamy badania fazy I, II oraz III, a na etapie po rejestracyjnym – badania fazy IV. Informacje z badań we wcześniejszej fazie służą do planowania badań w późniejszej fazie [8]. Celem badań fazy I jest ocena bezpieczeństwa i tolerancji zakresu dawek, które będą testowane w kolejnych etapach, a także scharakteryzowanie farmakokinetyki i farmakodynamiki.

W badaniach fazy I zazwyczaj biorą udział zdrowi ochotnicy, jednak w niektórych obszarach medycyny, takich jak onkologia, większość badań fazy I obejmuje pacjentów, którzy wyczerpali inne możliwości leczenia. Udział w badaniu jest ich ostatnią szansą na kontrolę choroby [13]. Faza II ma na celu zbadanie bezpieczeństwa i skuteczności produktu badanego w populacji docelowej, dla której jest on przeznaczony, aby lepiej scharakteryzować zależność dawka-odpowiedź. Badania fazy III są prowadzone w celu potwierdzenia, czy terapia eksperymentalna oferuje korzyści kliniczne dla określonej populacji (najczęściej w porównaniu do innych terapii stosowanych w praktyce klinicznej) i dalszego zbadania jej profilu bezpieczeństwa. Badania fazy IV (tzw. badania po rejestracji) są prowadzone po dopuszczeniu nowej terapii do obrotu. Gromadzą one dodatkowe informacje na temat skutków ubocznych i bezpieczeństwa oraz długoterminowych zagrożeń i korzyści wynikających ze stosowania terapii [8, 13].

Tradycyjne (konwencjonalne) badania kliniczne są projektowane z ustaloną maksymalną liczebnością próby i ustaloną liczbą interwencji. Dane z badań klinicznych są analizowane, gdy badania są zakończone po osiągnięciu z góry określonej wielkości próby. Konwencjonalne projekty badań klinicznych zwykle nie przewidują modyfikacji głównych elementów projektu badania (np. wielkości próby czy rodzaju ocenianej interwencji) w czasie trwania badania [8]. Obecnie jesteśmy jednak świadkami ewolucji tradycyjnego modelu prowadzenia badań klinicznych. Rozwój technologii oraz nowych metod badawczych sprzyja wprowadzaniu coraz bardziej złożonych modeli badawczych. Obok tradycyjnych modeli badawczych coraz większą rolę ogrywają badania kliniczne o modelu adaptacyjnym [9].

Adaptacyjne badania kliniczne to badania, w których projekt może zostać zmieniony w trakcie ich trwania w oparciu o zgromadzone i analizowane dane [8, 9]. Takie zaplanowane modyfikacje są opisane w dokumentacji badania przed rozpoczęciem rekrutacji uczestników. W tradycyjnych modelach badawczych modyfikacje nie są wcześniej planowane i wynikają z konieczności ich wprowadzenia (np. w zakresie zmiany kryteriów kwalifikacji uczestników). Zaplanowane zmiany w adaptacyjnych badaniach klinicznych mogą obejmować między innymi: zmianę wielkości próby, zmianę proporcji przydziału uczestników do ramion badania, identyfikację grupy badanej z największym prawdopodobieństwem odniesienia korzyści i skupienie na nich wysiłków rekrutacyjnych, zatrzymanie całego badania na wczesnym etapie w przypadku uzyskania danych o braku skuteczności testowanych interwencji, badania mogą zostać przedłużone z fazy I do fazy II lub z fazy II do fazy III w ramach jednego protokołu badawczego lub ramiona leczenia mogą zostać dodane lub usunięte [14]. To podejście może ograniczyć wykorzystanie zasobów, skrócić

czas trwania badania i zwiększyć prawdopodobieństwo, że wyniki badania będą miały istotną wartość naukową lub kliniczną. Badania kliniczne o modelu adaptacyjnym wymagają jednak rygorystycznego podejścia w planowaniu analizy danych okresowych, która jest podstawą dokonywanych modyfikacji, tak aby zapewnione były poprawność statystyczna i integralność badania [8].

Adaptacyjne modele badawcze są szeroko wykorzystywane w obszarze onkologii [10, 15]. Rozwój wiedzy w zakresie coraz bardziej złożonych aspektów biologii nowotworów spowodował zmiany w projektowaniu badań klinicznych. Badania kliniczne w onkologii odeszły od tradycyjnych badań oceniających chemioterapię cytotoksyczną w populacjach cechujących się wyłącznie określonym typem histologicznym nowotworu [10]. Coraz większą rolę odgrywają adaptacyjne i oparte na biomarkerach badania kliniczne testujące leki ukierunkowane molekularnie (takie jak terapie celowane lub immunoterapie). Ich przykładem są badania kliniczne parasolowe (ang. *umbrella clinical trials*) i koszykowe (ang. *basket clinical trials*). Badania koszykowe i badania parasolowe wykorzystują testy molekularne, które umożliwiają rekrutację uczestników z określonymi typami zmian molekularnych w obrębie nowotworu [16]. W badaniu klinicznym parasolowym testuje się skuteczność nowych produktów leczniczych u uczestników z tym samym typem nowotworu, ale różnymi mutacjami (zmianami) genów lub biomarkerami. Uczestnicy badania otrzymują leczenie w oparciu o konkretną mutację lub biomarker wykryty w ich nowotworze. Przykładem badania o modelu parasolowym jest Lung-MAP (NCT02154490) [17]. Badania kliniczne koszykowe mają na celu sprawdzenie, na ile bezpieczny i skuteczny jest nowy lek lub inna substancja u uczestników cierpiących na różne rodzaje nowotworów, u których występuje ta sama mutacja lub biomarker. Przykładem badania o modelu koszykowym jest NCI-MATCH (NCT02465060) [18]. Badania kliniczne koszykowe i parasolowe są zwykle projektami wieloetapowymi, wieloramiennymi, pozwalają na równoczesne testowanie wielu terapii. Rekrutacja uczestników może zostać przerwana w ramionach testujących terapie, które nie wykazują wystarczającej aktywności. Ponadto nowe terapie mogą zostać dodane do badania bez konieczności projektowania i uruchamiania nowego, oddzielnego badania [10].

Innym przykładem badań adaptacyjnych powszechnie stosowanych w onkologii są badania kliniczne o modelu ciągłym lub płynnym (nomenklatura w języku polskim nie jest spójna i stanowi tłumaczenie z ang. *seamless clinical trials*) [19]. W przeciwieństwie do tradycyjnego modelu prowadzenia badań klinicznych, w którym każda faza – od fazy I do fazy III – prowadzona jest oddzielnie, badania kliniczne o modelu ciągłym łączą dwie lub więcej faz w jedno badanie

z płynnym przejściem między nimi w oparciu o wcześniej określone kryteria [8]. Podejście to stosuje się zwłaszcza w badaniach wczesnej fazy, a jego wykorzystanie jest motywowane potrzebą przyspieszenia opracowywania leków onkologicznych poprzez zajęcie się wieloma pytaniami naukowymi (klinicznymi) w ramach jednego badania klinicznego [19]. W rezultacie coraz powszechniejsze są badania kliniczne fazy I/II, które w obrębie tego samego protokołu badawczego uwzględniają fazę I obejmującą zwykle etap ustalania dawki i fazę II, w ramach której zbierane są dodatkowe dane na temat efektywności badanej substancji w dodatkowej grupie uczestników. Badania fazy I/II mają na celu określenie optymalnej dawki, a także schematu leczenia, który zostanie wykorzystany do oceny w późniejszej fazie. Są szczególnie przydatne w sytuacjach, w których pożądana jest szybka ocena zarówno bezpieczeństwa, jak i skuteczności nowego leku. Nie bez znaczenia są również kompleksowe badania fazy I, które w swojej strukturze często przypominają badania fazy I/II [19, 20]. W badaniach tych etapowi ustalania dawki (ang. *dose escalation*) towarzyszy etap ekspansji (ang. *dose expansion*), którego celem jest włączenie dodatkowych kohort uczestników w celu lepszego scharakteryzowania profilu bezpieczeństwa badanego produktu leczniczego oraz oceny interwencji w obrębie populacji charakteryzujących się wybranymi cechami [21]. Coraz więcej mówi się także o badaniach fazy II/III w późnej fazie rozwoju leków onkologicznych, które wspierają podejmowanie decyzji regulacyjnych [22, 23].

Zmiany jakie obserwujemy w obszarze badań klinicznych są także efektem nowych wyzwań, przed którymi staje środowisko badawcze. Pandemia COVID-19 i wcześniejsze globalne zagrożenia dla zdrowia publicznego pokazały, że jest możliwe przyspieszenie badań klinicznych. W wyjątkowych okolicznościach pandemii COVID-19 agencje regulacyjne priorytetowo traktowały badania kliniczne mające na celu zbadanie metod diagnostycznych, leczenia i zapobiegania COVID-19 [24]. Pandemia COVID-19 przyczyniła się do rozwoju adaptacji i innowacji metodologicznych w zakresie badań klinicznych. Duża liczba interwencji do sprawdzenia doprowadziła m.in. do powszechniejszego wykorzystania badań klinicznych platformowych [25, 26]. Badania platformowe, w porównaniu do tradycyjnych dwuramiennych badań klinicznych, umożliwiają równoczesną ocenę wielu interwencji w porównaniu do wspólnej grupy kontrolnej. Często mają one charakter adaptacyjny, pozwalają na dodanie nowych interwencji i zmianę grupy kontrolnej w trakcie trwania badania. W przeglądzie badań platformowych prowadzonych w czasie pandemii COVID-19 ustalono, że w od stycznia 2020 r. do maja 2021 r. uruchomionych zostało 58 badań platformowych oceniających interwencje w zakresie leczenia i profilaktyki COVID-19 [27]. Dla porównania, w latach 2001–2019 rozpoczęto 16 platformowych badań klinicznych [16, 27]. Niektóre badania kliniczne, które były

uruchomione jeszcze przed wybuchem pandemii COVID-19 zaadoptowano do oceny skuteczności i bezpieczeństwa interwencji w leczeniu COVID-19. Przykładem jest badanie REMAP-CAP (NCT02735707) [28, 29]. Jest to badanie o modelu adaptacyjnym, które zostało uruchomione w 2016 roku w celu oceny szeregu interwencji w zakresie leczenia pacjentów przyjmowanych na oddział intensywnej terapii z pozaszpitalnym zapaleniem płuc. Pierwszego uczestnika z COVID-19 włączono do badania REMAP-CAP w marcu 2020 r., niecałe 6 tygodni po tym, jak Światowa Organizacja Zdrowia (ang. *World Health Organization*, WHO) uznała COVID-19 za zagrożenie zdrowia publicznego o zasięgu międzynarodowym [30]. Repozycjonowanie leków (ang. *drug repurposing*) – wykorzystanie leku wcześniej zatwierdzonego (dopuszczonego do obrotu) w celu oceny w zakresie nowego wskazania – także przyczyniło się do przyspieszenia identyfikacji postępowania terapeutycznego w leczeniu COVID-19. Odkrywanie nowych zastosowań terapeutycznych dla leków, które pierwotnie były przeznaczone do innych celów może pomóc rozszerzyć zakres dostępnych dla pacjentów opcji leczenia w sposób efektywny pod względem wykorzystania zasobów. Badacze mogą wykorzystać m.in. istniejącą wiedzę na temat profili bezpieczeństwa leków, skuteczności, aktywności farmakokinetycznej i innych cech [31]. W pierwszej połowie 2020 roku około dwie trzecie badań nad COVID-19 testowało lek dopuszczony do obrotu w innym wskazaniu [32].

Nowe modele prowadzenia badań klinicznych stwarzają wiele możliwości, ale jednocześnie wiążą się z istotnymi wyzwaniami dla środowiska badań klinicznych. Wraz z ich coraz powszechniejszym wykorzystaniem konieczne jest kształtowanie nowych i aktualizowanie istniejących regulacji w zakresie badań klinicznych. Fundamentem prowadzenia badań klinicznych jest ocena etyczna, która odnosi się zarówno do ochrony uczestników badań klinicznych, jak i do oceny rzetelności tych badań [5]. Zasady oceny etycznej badań klinicznych są zbudowane na podstawie regulacji i wytycznych zawartych w dokumentach takich jak [5, 33]:

- Kodeks Norymberski,
- Deklaracja Helsińska Światowego Stowarzyszenia Lekarzy,
- Międzynarodowe Wytyczne w Zakresie Etyki Badań nad Zdrowiem z Udziałem Ludzi opracowane przez Radę Międzynarodowych Organizacji Nauk Medycznych (ang. *Council for International Organizations of Medical Sciences*, CIOMS) we współpracy z WHO,
- U.S. Common Rule,

- Rozporządzenie Parlamentu Europejskiego i Rady (UE) Nr 536/2014 z dnia 16 kwietnia 2014 r. w sprawie badań klinicznych produktów leczniczych stosowanych u ludzi (ang. *European Union Clinical Trials Regulation* (Regulation (EU) No 536/2014)),
- Dobra Praktyka Kliniczna (ang. *Good Clinical Practice*) opracowana przez Międzynarodową Radę Harmonizacji Wymagań Technicznych dla Rejestracji Produktów Leczniczych Stosowanych u Ludzi (ang. *International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use*).

Etyczne badania kliniczne mają na celu dostarczanie naukowo uzasadnionych odpowiedzi na istotne pytania badawcze i kliniczne. Ich rolą jest sprawiedliwy dobór uczestników, respektowanie praw i dobrostanu uczestników ze szczególnym uwzględnieniem właściwej komunikacji z uczestnikami na temat prowadzonego badania i świadomej zgody. Ważne jest zachowanie zasad przejrzystości poprzez rejestrację badania klinicznego w publicznie dostępnym rejestrze badań klinicznych oraz terminowe udostępnianie wyników badań (niezależnie od tego czy wyniki te są pozytywne czy negatywne). Nie bez znaczenia jest także wykonalność oraz możliwość przeprowadzenia badania w oparciu o istniejące zasoby, jak również odpowiednie zapewnienie jakości poprzez niezależną ocenę przez organy regulatorowe i nadzór. Zarządzanie jakością powinno być uwzględniane na wszystkich etapach badań klinicznych: od przygotowania projektu aż do zakończenia realizacji badania [5, 34].

Liczne dane literaturowe wskazują, że znaczna część badań klinicznych jest obarczona wadami w zakresie projektu badania, wykonania, analizy i raportowania danych badawczych oraz wyników, co rodzi wątpliwości natury etycznej [6]. Przyspieszenie badań klinicznych i opracowanie nowych modeli badań klinicznych może być bardzo korzystne, ale może też generować i pogłębiać powszechne problemy w zakresie etyki badań i rzetelności badawczej.

6.2 Cel pracy

Głównym celem prac badawczych była **analiza wybranych aspektów etycznych badań klinicznych, w których zastosowano tzw. akceleratory metodologiczne i organizacyjne**. Akceleratory metodologiczne i organizacyjne w kontekście niniejszej pracy doktorskiej odnoszą się do nowych rozwiązań w zakresie projektowania i metodologii badań klinicznych oraz usprawnień instytucjonalnych i regulacyjnych. Celem ich stosowania jest prowadzenie szybszych, bardziej zoptymalizowanych i skoncentrowanych na pacjencie badań klinicznych.

Prace badawcze podzielono na dwa etapy. W **pierwszym etapie** dokonano analizy wybranych aspektów etycznych badań klinicznych testujących metody leczenia i zapobiegania COVID-19: Sformułowano następujące cele szczegółowe:

- analiza informatywności badań klinicznych, rozpoczętych w pierwszych sześciu miesiącach pandemii i zarejestrowanych w rejestrze *ClinicalTrials.gov* (publikacja *„How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov”* (**P1**)),
- analiza wyzwań etycznych związanych z uruchomieniem badań klinicznych w celu oceny bezpieczeństwa i skuteczności leków dopuszczonych do obrotu w innym wskazaniu (publikacja *„Ethical challenges of clinical trials with a repurposed drug in outbreaks”* (**P2**)).

W **drugim etapie** dokonano analizy wybranych aspektów etycznych nowych modeli badań klinicznych w obszarze onkologii. Sformułowano następujące cele szczegółowe:

- analiza ryzyka i korzyści koszykowych badań klinicznych w onkologii (publikacja *„Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis”* (**P3**)),
- analiza cech i raportowania badań klinicznych o modelu ciągłym stosowanych we wczesnej fazie rozwoju leków w onkologii (publikacja *„Seamless trials in oncology: A cross-sectional analysis of characteristics and reporting”* (**P4**)).

6.3 Materiał i metody badawcze

6.3.1 Zaangażowane jednostki badawcze

Badania zrealizowano w interdyscyplinarnym zespole badawczym *Research Ethics in Medicine Study Group* (REMEDY) w Zakładzie Bioetyki Uniwersytetu Jagiellońskiego Collegium Medicum pod kierownictwem dr. hab. Marcina Waligóry, prof. UJ.

Publikacje *„How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov”* (**P1**) oraz *„Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis”* (**P3**) powstały we współpracy z międzynarodowymi jednostkami badawczymi.

Do zespołu badawczego w ramach badań do publikacji **P1** należeli: prof. Jonathan Kimmelman i dr Nora Hutchinson z *McGill University* (Kanada) oraz dr Benjamin Gregory Carlisle z *Berlin Institute of Health at Charité* (Niemcy).

Badania do publikacji **P3** zrealizowano we współpracy z dr. Simonem Van Wambeke – onkologiem ze szpitala *Ziekenhuis Netwerk Antwerpen (ZNA)* (Belgia).

6.3.2 Metody, techniki i narzędzia badawcze

Rozprawa doktorska obejmuje trzy publikacje o charakterze meta-badań (**P1**, **P3**, **P4**) oraz jedną publikację o charakterze analizy normatywnej (**P2**).

Meta-badania to interdyscyplinarna dziedzina nauki, często określana jako „badania nad badaniami” [35]. Meta-badania korzystają z tzw. danych zastanych i opierają się o metody analizy i syntezy danych. Wykorzystują różne techniki metodologiczne, aby dostarczać danych empirycznych na temat procesu badawczego [35, 36]. Celem meta-badań jest ocena i udoskonalanie praktyk badawczych. Od pewnego czasu meta-badania z powodzeniem są stosowane do oceny zagadnień bioetycznych związanych z prowadzeniem badań klinicznych. Przykładami meta-badań w bioetyce są m.in. analizy dotyczące ryzyka i korzyści jakie odnoszą uczestnicy biorący udział w badaniach klinicznych, wartości społecznej prowadzenia badań klinicznych, czy raportowania wyników badań klinicznych [37-42].

Publikacja *„How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov”* (**P1**) i *„Seamless trials in oncology: A cross-sectional analysis of characteristics and reporting”* (**P4**) to analizy

wykonane w oparciu o dane dostępne w międzynarodowym rejestrze badań klinicznych – *ClinicalTrials.gov*. Rejestr *ClinicalTrials.gov* to internetowa baza danych i repozytorium informacji o badaniach klinicznych oraz ich wynikach, prowadzona przez amerykański Narodowy Instytut Zdrowia (ang. *National Institute of Health*, NIH) [43]. Z jednej strony rejestr ten umożliwia wyszukiwanie informacji na temat prowadzonych na świecie badań klinicznych. Z drugiej strony, informacje zawarte w rejestrze są podstawą licznych analiz na temat metodologii, charakterystyki oraz raportowania wyników badań klinicznych [43, 44]. Rejestr ten obejmuje informacje na temat rozpoczętych, trwających oraz zakończonych badań klinicznych. Status badania może być na bieżąco aktualizowany przez podmioty odpowiedzialne za badania kliniczne.

Publikacja *„Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis"* (**P3**) to przegląd systematyczny z metaanalizą wykonany zgodnie z metodyką zaproponowaną w opracowaniu *Cochrane Handbook for Systematic Reviews of Interventions* [45]. W tym meta-badaniu zostały przeanalizowane wyniki badań klinicznych z artykułów naukowych odnalezionych w bazach Embase i PubMed oraz wyniki zaraportowane w rejestrze *ClinicalTrials.gov*.

Meta-badania zostały zrealizowane zgodnie z prospektywnie zarejestrowanymi protokołami badawczymi (**Tabela 1**) [46-48]. Protokoły badawcze szczegółowo prezentują metodykę poszczególnych meta-badań. Czynności badawcze po opracowaniu protokołu badawczego dla każdego z meta-badań obejmowały przeszukanie baz danych zgodnie ze strategią wyszukiwania, selekcję danych zgodnie z kryteriami włączenia i wyłączenia, ekstrakcję danych, syntezę i analizę wyników oraz przygotowanie manuskryptu. W celu zwiększenia wiarygodności etap selekcji oraz ekstrakcji danych realizowało dwóch niezależnych badaczy, a wszelkie niezgodności były rozwiązywane na drodze dyskusji.

Standardy raportowania zostały dobrane odpowiednio do typu badania. Wyniki publikacji **P1** oraz **P4** zostały zaprezentowane zgodnie z wytycznymi STROBE (ang. *Strengthening the Reporting of Observational Studies in Epidemiology*) [49], a wyniki publikacji **P3** zgodnie z wytycznymi PRISMA (ang. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020*) [50].

Artykuł *„Ethical challenges of clinical trials with a repurposed drug in outbreaks"* (**P2**) ma charakter analizy normatywnej. Analiza normatywna polega na przedstawieniu i ewaluacji argumentów oraz przedstawieniu rekomendacji w ramach pewnego zbioru norm lub wartości [51].

W publikacji **P2** wykorzystano technikę studium przypadku do przedstawienia wyzwań etycznych i rekomendacji związanych z prowadzeniem badań klinicznych nad lekiem już dopuszczonym do obrotu, który testowany jest pod kątem nowego wskazania (jest tzw. repozycjonowanie leków). Analiza ta dotyczy badań klinicznych w czasie kryzysów zdrowotnych, których przykładem była pandemia COVID-19.

6.3.3 Opracowanie statystyczne wyników

Analizy statystyczne wykonano przy użyciu oprogramowania *R Project for Statistical Computing* (wersja 3.6.3 – publikacja **P1**, wersja – 4.3.2 publikacja **P3**) oraz *IBM SPSS Statistics for Window*s, wersja 28.0. (2021) (publikacja **P4**). Dodatkowym oprogramowaniem wspomagającym był *Microsoft Excel*. Szczegółowy opis wykorzystanych metod statystycznych został przedstawiony w poszczególnych artykułach w części metodycznej. W ramach publikacji **P2** nie były wykonywane analizy statystyczne.

6.3.4 Aspekty etyczne

Badania zrealizowano w oparciu o publicznie dostępne bazy danych. Badania nie obejmowały interakcji z uczestnikami badań klinicznych. Zebrane i przetworzone dane badawcze w ramach meta-badań zostały udostępnione w otwartym dostępie, zgodnie z zasadami otwartej nauki, na platformie *Open Science Framework* (dane dostępu przedstawiono w **Tabeli 1**).

Tabela 1. Dane badawcze powiązane z opublikowanymi artykułami zamieszczone w otwartym dostępie

Tytuł publikacji	**Protokół badawczy (platforma, referencja)**	**Dane badawcze (platforma, referencja)**
How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov	Open Science Framework [47]	Open Science Framework [47]
Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis	PROSPERO CRD42023406401 [46]	Open Science Framework [52]
Seamless trials in oncology: A cross-sectional analysis of characteristics and reporting	Open Science Framework [48]	Open Science Framework [48]

6.4 Wyniki

6.4.1 Etyczne aspekty prowadzenia badań klinicznych w czasie pandemii COVID-19

Charakter i złożoność pandemii stwarzają szereg istotnych wyzwań etycznych w zakresie prowadzenia badań naukowych w dziedzinie zdrowia [53]. Zapobieganie i zarządzanie sytuacjami kryzysowymi w zakresie zdrowia publicznego wyzwalają etyczny obowiązek szybkiego przeprowadzenia rygorystycznych badań klinicznych. Głównym celem takich badań powinna być ocena, które interwencje są bezpieczne i skuteczne w leczeniu lub zapobieganiu chorobie lub stanowi związanemu z kryzysem [54]. Z drugiej strony, prowadzone badania mają na celu zapobiegać rozprzestrzenianiu się niesprawdzonych interwencji, które są niebezpieczne lub nieskuteczne. Globalna pandemia COVID-19 doprowadziła do uruchomienia w krótkim czasie bardzo dużej liczby badań klinicznych. Szybko jednak pojawiły się obawy, że pospieszne i nieskoordynowane wysiłki badawcze doprowadzą do rozpoczęcia badań o ograniczonym potencjale generowania wiarygodnych dowodów naukowych, prowadząc do zjawiska zwanego marnotrawstwem badawczym (ang. *research waste*) [24]. Dodatkowo dynamicznie wzrosło awaryjne stosowanie interwencji poza ich zarejestrowanymi wskazaniami (ang. *off-label use*). Stosowanie leków niezgodnie z przeznaczeniem leczniczym było powszechne, szczególnie w początkowej fazie pandemii COVID-19, co również budziło pytania dotyczące bezpieczeństwa pacjentów i wątpliwości natury etycznej, takie jak sprawiedliwy dostęp do zasobów medycznych [55].

6.4.1.1 Analiza informatywności badań klinicznych

Publikacja *„How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov”* (**P1**) [1] to systematyczna analiza informatywności badań klinicznych testujących metody leczenia i zapobiegania chorobie COVID-19. Informatywność, w kontekście badań klinicznych określa, czy badanie jednoznacznie odpowie na postawione pytania badawcze i czy wesprze podejmowanie decyzji klinicznych [56]. Sformułowano pięć warunków, które należy spełnić, aby badanie kliniczne mogło zostać uznane za informatywne [24, 56]:

1. Badanie kliniczne powinno testować istotne klinicznie pytanie badawcze, które nie zostało dotąd rozwiązane (kryterium 1).
2. Badanie klinicznie powinno być zaprojektowane tak, aby dostarczało wiarygodnej odpowiedzi na postawione pytanie badawcze (kryterium 2).

3. Badanie kliniczne powinno być wykonalne w zakresie celów rekrutacyjnych oraz czasu trwania (kryterium 3).
4. Wyniki badania klinicznego powinny być analizowane w sposób, który wspiera ich prawidłową interpretację (kryterium 4).
5. Wyniki badań klinicznych powinny być udostępniane w odpowiednim czasie, w zgodzie z obowiązującymi regulacjami (kryterium 5).

W publikacji *„How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov”* (**P1**) dokonano analizy informatywności badań klinicznych testujących skuteczność interwencji w zapobieganiu oraz leczeniu COVID-19, które były uwzględnione w rejestrze *ClinicalTrials.gov* i uruchomione od stycznia 2020 do czerwca 2020. Jest to pierwsze badanie oceniające informatywność badań klinicznych uruchomionych w związku z pandemią COVID-19. Na potrzeby badania opracowano zastępcze miary informatywności badania klinicznego, tak aby w oparciu o dane dostępne w rejestrze, możliwe było określenie czy kryteria informatywności zostały spełnione. Przyjęto następujące miary:

a) Badanie kliniczne nie było wtórne, a więc testowało inne pytanie badawcze niż wcześniej uruchomione badania (wskaźnik ważności hipotezy badawczej – kryterium 1). Oceny dokonano na podstawie porównania fazy badania, typu badania (leczenie/profilaktyka), charakterystyki uczestników badania, testowanej interwencji, grupy kontrolnej oraz pierwszorzędowych punktów końcowych.
b) Badanie kliniczne było dobrze zaprojektowane (kryterium 2). Oceny dokonano w oparciu o informacje na temat fazy badania, randomizacji, obecności grupy kontrolnej, zaślepienia badania, punktów końcowych ocenianych w badaniu oraz włączenia uczestników w wieku 60 lat (lub więcej).
c) Rekrutacja uczestników do badania była wykonalna w zakresie zaplanowanego czasu trwania rekrutacji oraz osiągnięcia zakładanych celów rekrutacyjnych (kryterium 3).

Większość (86%) z analizowanych badań klinicznych w przyjętym czasie obserwacji (tj. sześć miesięcy od momentu uruchomienia badania) nie była zakończona. Dlatego zrezygnowano z uwzględniania pozostałych dwóch kryteriów dotyczących wyników (kryterium 4 i 5), co stanowiło jedno z ograniczeń badania.

W artykule przedstawiono ogólną proporcję badań spełniających wszystkie trzy przyjęte kryteria informatywności (potencjalna wtórność, jakość projektu i wykonalność rekrutacji uczestników). Zaprezentowano także dane indywidualnie dla każdego z ocenianych kryteriów.

Wyjściowa liczba badań, które oceniano podczas procesu selekcji wyniosła 521. W ostatecznej analizie uwzględniono 500 badań klinicznych (tj. 21 badań nie spełniło kryteriów włączenia). Liczba ta wynikała z kompleksowego przeszukania rejestru badań klinicznych i nie została z góry ustalona. Odsetek potencjalnie wtórnych badań w analizowanej kohorcie wyniósł 4,1%. Ponad połowa badań (56,2%) nie spełniała kryteriów wysokiej jakości projektu badania (uwidaczniając problemy z zakresie braku randomizacji, braku grupy kontrolnej, braku zaślepienia, wykorzystania punktu końcowego niezgodnego z rekomendacjami lub niewłączenia populacji szczególnie narażonej na infekcję COVID-19). Odsetek badań, w których rekrutacja uczestników była niewykonalna, wyniósł 22,6%. Do oceny wszystkich trzech kryteriów zakwalifikowano 194 badania. Wykazano, że zaledwie jedna trzecia badań (29,9%) spełniła wszystkie trzy kryteria informatywności.

Znajomość częstości występowania nieinformatywnych badań klinicznych przeprowadzonych na wczesnych etapach pandemii może pomóc w motywowaniu do opracowania skuteczniejszej polityki badawczej w oczekiwaniu na przyszłe kryzysy zdrowia publicznego. Niedociągnięcia w projektowaniu badań, wykonalności rekrutacji i potencjalnej wtórności badań klinicznych odzwierciedlają długotrwałe słabości środowiska badań klinicznych, które prawdopodobnie zostały wzmocnione przez wyjątkowe okoliczności pandemii.

6.4.1.2 Analiza wyzwań etycznych związanych z uruchomieniem badań klinicznych w celu oceny skuteczności leków dopuszczonych do obrotu w innym wskazaniu

W publikacji *„Ethical challenges of clinical trials with a repurposed drug in outbreaks”* (**P2**) [2] dokonano analizy wyzwań etycznych związanych z projektowaniem badań klinicznych dla leków o zmienionym przeznaczeniu. W publikacji opisano przykład amantadyny. Amantadyna jest lekiem stosowanym w lecznictwie od lat 60 XX wieku. Lek ten znajduje zastosowanie w leczeniu objawów choroby Parkinsona, był także stosowany w łagodzeniu objawów grypy typu A. W czasie pandemii COVID-19 amantadyna (głównie w Polsce) wzbudziła ogromne zainteresowanie jako potencjalny środek leczniczy. Popularność leku stymulowała głośna publiczna debata. Pomimo braku dowodów na skuteczność i negatywnych rekomendacji środowisk naukowych, w Polsce amantadyna była na szeroką skalę przepisywana pacjentom

chorującym na COVID-19. W konsekwencji zostały wprowadzone ograniczenia w ordynowaniu i wydawaniu produktu leczniczego – leku *Viregyt K*, który zawierał chlorowodorek amantadyny.

W odpowiedzi na ogromne zainteresowanie społeczne lekiem, Agencja Badań Medycznych (ABM) sfinansowała dwa badania kliniczne - COV-PREVENT (NCT04854759) [57] oraz TITAN (NCT04952519) [58], których celem była ocena skuteczności amantadyny w leczeniu i zapobieganiu COVID-19. W artykule, wykorzystując przykład amantadyny, podjęto dyskusję czy zasadne było uruchomienie badań klinicznych oceniających amantadynę. Odwołano się do ram etycznych dotyczących ustalania priorytetów w zakresie uruchamiania badań klinicznych zaproponowanych w czasie pandemii COVID-19 przez Meyer i współpracowników [59]. Wskazano m.in na wątpliwości dotyczące spełnienia kryteriów ważności naukowej (ang. *scientific validity*) i jakości dowodów potwierdzających hipotezę badawczą. Z drugiej strony podkreślilono wysoką wartość społeczną z uwagi na potrzebę uzyskania solidnych dowodów weryfikujących skuteczność amantadyny, aby wesprzeć proces podejmowania decyzji klinicznych i uspokajając obawy opinii publicznej.

Artykuł ma charakter analizy normatywnej. Wykorzystując ten przykład, zilustrowano uniwersalne mechanizmy, które występowały podczas pandemii COVID-19. Wiele z dopuszczonych do obrotu interwencji szybko stało się przedmiotem badań klinicznych, jednocześnie jednak towarzyszyło temu równoległe stosowanie leku poza wskazaniami. Tak było m.in. z hydroksychlorochiną, która ostatecznie okazała się lekiem nieskutecznym w leczeniu COVID-19 [60]. W analizie podkreślono znaczenie wysokiej jakości dowodów naukowych w kontekście walki z dezinformacją, równocześnie rozważając potencjalne zagrożenia związane z niekontrolowanym wykorzystaniem leku, którego działanie nie zostało udowodnione. Niekontrolowane wykorzystanie leków poza wskazaniami często odbija się negatywnie na jego dostępności czy wykorzystaniu leków zgodnie ze wskazaniami i zwiększa w ten sposób niesprawiedliwy dostęp do ograniczonych zasobów medycznych.

6.4.2 Nowe modele prowadzenia badań klinicznych w onkologii: wybrane zagadnienia etyczne

Nowe modele badań klinicznych w onkologii stwarzają możliwość szybszego opracowywania leków i zapewnienia pacjentom dostępu do nowych metod leczenia, ale wiążą się z nimi także wyzwania [20, 21, 61]. Ich rozwojowi towarzyszą debaty na temat tego, czy takie badania oferują etyczne i metodologiczne korzyści w porównaniu z tradycyjnymi badaniami. W badaniu opublikowanym na łamach czasopisma *BMC Medical Ethics* w 2019 roku przedstawiono m.in. dyskusję na temat wyzwań etycznych badań parasolowych i badań koszykowych w medycynie precyzyjnej [61]. Wskazano m.in. na wątpliwości etyczne dotyczące ważności naukowej, sprzyjającego stosunku ryzyka do korzyści i świadomej zgody uczestników. Inni autorzy odnieśli się do również do wyzwań związanych z raportowaniem badań klinicznych o modelu ciągłym [20]. Dlatego, postanowiono zweryfikować hipotezy stawiane w analizach teoretycznych opierając się na danych badawczych zebranych w meta-badaniach. Wykonano analizę ryzyka i korzyści dla badań koszykowych w onkologii oraz raportowania badań klinicznych o modelu ciągłym stosowanych we wczesnej fazie rozwoju leków w onkologii.

6.4.2.1 Analiza ryzyka i korzyści dla badań koszykowych w onkologii

Jednym z podstawowych wymogów etycznych prowadzenia badań klinicznych jest właściwy stosunek ryzyka i korzyści dla uczestników. Ryzyko związane z udziałem w badaniach klinicznych powinno być uzasadnione perspektywą korzyści dla uczestników (jeśli takie istnieją) oraz perspektywą poszerzenia wiedzy medycznej. W publikacji *„Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis”* (**P3**) [3] wykorzystano podejście meta-badawcze, aby dostarczyć danych na temat ryzyka i korzyści jakie odnoszą uczestnicy badań koszykowych w onkologii. Projekt stanowił kontynuację serii analiz prowadzonych przez zespół REMEDY na temat ryzyka i korzyści związanych z różnymi typami badań klinicznych w onkologii. Poprzednie analizy dostarczyły danych na temat ryzyka i korzyści związanych z udziałem w pediatrycznych badaniach klinicznych fazy I [39] i II [62], a także w badaniach parasolowych [37] .

Badanie zostało prospektywnie zarejestrowane w bazie PROSPERO (CRD42023406401) [46]. Ryzyko zmierzono gromadząc dane na temat ciężkich zdarzeń niepożądanych związanych z leczeniem (stopnie 3, 4 i 5 wg skali *Common Terminology Criteria for Adverse Events* [63]), a korzyść na podstawie odsetka obiektywnych odpowiedzi (ang. *objective response rate*, ORR).

Wyekstrahowano i przeanalizowano również dane na temat czasu przeżycia wolnego od progresji (ang. *progression-free survival*, PFS) i czasu przeżycia całkowitego (ang. *overall survival*, OS).

Wykazano, że skumulowany wskaźnik ORR dla wszystkich 126 uwzględnionych badań wyniósł 18,0% (95% przedział ufności (ang. *confidence interval*, CI) 14,8-21,1). Mediana PFS wyniosła 3,1 miesiąca, a mediana OS – 8,9 miesiąca. Wskaźnik zgonów związanych z testowanym leczeniem wyniósł 0,7%. Wykazano, że 30,4% uczestników badania doświadczyło działań niepożądanych związanych z leczeniem stopnia 3–4.

W dyskusji przedstawiono porównanie uzyskanych wyników w odniesieniu do danych literaturowych na temat innych modeli badawczych stosowanych w onkologii. Wykazano, że trudno jednoznacznie odpowiedzieć, czy badania koszykowe są szansą dla uczestników w zakresie korzystniejszego profilu ryzyka i korzyści. Zaobserwowano jednak brak spójności w raportowaniu poszczególnych punktów końcowych. Wskaźniki ORR zaraportowano w 105 badaniach (83,3%), ale dane dotyczące mediany PFS i OS były dostępne tylko w 51 (40,5%) i 40 (31,7%) badaniach. Podobnie, tylko 56 badań (44,4%) upubliczniło dane na temat zgonów związanych z leczeniem, a 33 badania (26,2%) zgłosiły działania niepożądane stopnia ≥ 3. Mimo że analiza nie obejmuje wszystkich aspektów związanych z korzyściami i ryzykiem, zaproponowano podjęcie działań mających na celu zwiększenie częstotliwości raportowania danych umożliwiających przeprowadzenie analiz na ten temat.

6.4.2.2 Analiza cech i raportowanie badań klinicznych o modelu ciągłym stosowanych we wczesnej fazie rozwoju leków w onkologii

Nowe projekty badań klinicznych, zwłaszcza te, które proponują adaptacje i złożoną strukturę, stanowią wyzwanie dla przejrzystości badań klinicznych i ich wyników [64]. W publikacji *„Seamless trials in oncology: A cross-sectional analysis of characteristics and reporting”* (**P4**) [4] dokonano analizy badań klinicznych o modelu ciągłym stosowanych we wczesnej fazie rozwoju leków w onkologii, które zostały zarejestrowane w *ClinicalTrials.gov*. Dostarczono informacji na temat charakterystyki tychże badań oraz raportowania ich wyników w rejestrze. Znajomość tych danych jest istotna z uwagi na coraz częstsze wykorzystanie badań o modelu ciągłym w procesie opracowywania nowych leków przeciwnowotworowych.

Do analizy włączono 1051 badań, w tym 562 (53,5%) badań fazy I i 489 (46,5%) badań zarejestrowanych jako badania I/II. Większość badań testowała wiele leków (654, 62,2%) i dotyczyła nowotworów litych (752, 71,6%). Ponad połowa (530, 50,4%) oceniała więcej niż

jeden rodzaj nowotworu. Wykazano, że tylko 34,7% (365 z 1051) badań opublikowało wyniki w rejestrze *ClinicalTrials.gov*. Całkowity wskaźnik raportowania dla badań fazy I/II był ponad trzykrotnie wyższy niż dla badań fazy I. Zaledwie 24,0% badań miało upublicznione wyniki w rejestrze *ClinicalTrials.gov* w ciągu 24 miesięcy od daty zakończenia badania. W analizie wskazano, że należy podjąć wysiłki w celu dostosowania funkcjonalności bazy danych *ClinicalTrials.gov* do nowych modeli badań klinicznych. Spośród 365 badań, które upubliczniły wyniki w rejestrze, charakterystykę uczestników i dane dla analizowanych punktów końcowych przedstawiono indywidualnie dla każdego etapu badania dla 176 badań (48,2%). W 145 badaniach (39,7%) dane te zaraportowano łącznie (bez podziału na etap badania), a dla 17 (4,7%) badań wyniki dostępne były tylko dla pierwszego etapu. W przypadku 27 (7,4%) badań sposób raportowania był niespójny np. charakterystykę uczestników raportowano osobno dla każdego etapu, ale wyniki dla poszczególnych punktów końcowych łącznie.

Jedną z nadrzędnych kwestii, którymi należy się zająć przy wdrażaniu badań o modelu ciągłym jest dostosowanie funkcjonalności bazy danych *ClinicalTrials.gov*, tak aby możliwe było skuteczne uchwycenie cech poszczególnych etapów badania, zarówno w opisie charakterystyki badania, jak i w prezentacji wyników. Ponadto należy wprowadzić udoskonalenia, które pomogą odróżnić tradycyjne badania fazy I od badań fazy I spełniających kryteria badań o modelu ciągłym.

6.5 Dyskusja

Podstawowym celem badań prowadzonych z udziałem ludzi jest spełnienie wymogu wartości naukowej i społecznej, czyli dostarczenie wartościowej wiedzy i środków niezbędnych do poprawy jakości i długości życia ludzi [65]. Koszty ponoszone przez uczestników badań klinicznych, którzy dobrowolnie biorą w nich udział i akceptują nieodłączne ryzyko w zamian za postęp naukowy, powinny rekompensować proporcjonalne zyski generowane przez wartość społeczną i naukową tych badań [5, 66]. Zapobieganie marnotrawstwu badawczemu stanowi podstawowy wymóg etyczny prowadzenia wszystkich badań naukowych [66]. W przypadku badań z udziałem ludzi, w tym badań klinicznych zapobieganie marnotrawstwu jest szczególnie istotne, ponieważ eksperymenty te wiążą się z narażaniem uczestników na różne formy ryzyka. Marnotrawstwo badawcze może wystąpić na każdym etapie badania klinicznego, od momentu projektowania, aż po jego wdrożenie i raportowanie wyników [67].

Koncepcja informatywności badań klinicznych podkreśla potrzebę unikania nieefektywnych procedur i zwiększania efektywności w prowadzeniu badań klinicznych, tak aby można je było przeprowadzać na odpowiednią skalę i dostarczać wiarygodnych danych [5, 24, 56]. Rygorystyczne projektowanie badań klinicznych jest kluczowym warunkiem informatywności i unikania marnotrawstwa badawczego [24]. Zasady etyczne i naukowe wymagają, aby badania kliniczne dotyczyły ważnego zagadnienia i aby zapewniono zasoby niezbędne do ich przeprowadzenia [68]. Przeprowadzanie badań, co do których można było przewidzieć, że nie odpowiedzą na pytanie badawcze, jest marnotrawstwem zasobów, naruszeniem zaufania uczestników badania i naruszeniem zasad etyki badawczej [69]. Jednak, pomimo że badania kliniczne są ściśle regulowane, zgodność z wymogami regulacyjnymi nie gwarantuje, że badanie przyniesie dobrej jakości wyniki. Co więcej, zwraca się uwagę na brak systematycznego podejścia do określania wartości naukowej i wykonalności badań klinicznych przed ich rozpoczęciem i w trakcie ich trwania [68].

Podczas pandemii COVID-19 w globalnej rywalizacji o znalezienie skutecznych metod prewencyjnych i metod leczenia przeprowadzono nadzwyczajnie wysoką liczbę badań klinicznych w relatywnie krótkim czasie. Niesprawdzone metody leczenia były stopniowo zastępowane lekami, których skuteczność potwierdzono w badaniach klinicznych [70]. Do kluczowych sukcesów należało m.in. przyspieszone opracowanie szczepionek oraz wdrażanie i przeprowadzanie innowacyjnych projektów badawczych w rekordowo krótkim czasie (np. badanie RECOVERY i badanie REMAP-CAP) [26, 69, 71]. Jest to dowód na to, jak dobrze

i skutecznie może działać proces badawczy [13]. Jednak nie wszystkie badania przyniosły wyniki pozwalające na poprawę opieki nad pacjentem. Duża liczba badań klinicznych w połączeniu z presją czasu doprowadziła do nasilenia wielu problemów etycznych. Podczas pandemii COVID-19 doszło do wzmożonego marnotrawstwa w badaniach klinicznych [72]. Liczne badania kliniczne były zaprojektowane w sposób uniemożliwiający uzyskanie wiarygodnych odpowiedzi na zadane pytania badawcze, weryfikowały podobne hipotezy badawcze, a założenia co do celów rekrutacyjnych były trudne do osiągnięcia [25, 26, 71]. Dodatkowo wiele badań nadal rekrutowało uczestników długo po tym, jak testowane przez nie interwencje okazywały się nieskuteczne [73].

Artykuł *„How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov* (**P1**) będący składową niniejszej rozprawy wskazuje, że zaledwie jedna trzecia badań uruchomionych w początkowym okresie pandemii COVID-19 spełniała kryteria w zakresie wysokiej jakości projektu badania, ważności testowanej hipotezy badawczej oraz wykonalności celów rekrutacyjnych i zaplanowanego czasu trwania badania [1]. Inna analiza wykazała, że od marca do października 2020 r. rozpoczęto ponad 2000 badań nad lekami stosowanymi w leczeniu COVID-19, ale tylko 5% z nich było randomizowanych i miało wystarczającą moc statystyczną, aby dostarczyć rzetelnych wyników [74]. Udowodniono także, że większość badań klinicznych z rejestru *ClinicalTrials.gov* w ciągu pierwszych 6 miesięcy pandemii nie doczekała się publikacji wyników lub została przerwana (dane te weryfikowano w okresie około 3 lat od daty rejestracji badania) [75]. Problemy zaobserwowane w badaniach klinicznych nad COVID-19 ilustrują ogólne wyzwania związane z projektowaniem i prowadzeniem badań klinicznych [69]. W innym badaniu, w którym analizowano randomizowane badania kliniczne (uwzględniając badania prowadzone w trzech wskazaniach chorobowych takich jak choroba niedokrwienna serca, cukrzyca i rak płuc) wykazano, że tylko 26,4% badań spełniało kryteria informatywności [6]. W rezultacie ponad 30% uczestników brało udział w badaniach, które prawdopodobnie nie dostarczyły dowodów wspierających decyzje kliniczne. Wykazano również, że odsetek informatywnych badań klinicznych nie różnił się istotnie pomiędzy analizowanymi jednostkami chorobowymi [6].

Proponowane są różne działania, aby zwiększyć informatywność badań klinicznych [73, 76]. Szczegółowe rekomendacje, jak ograniczyć nieinformatywne badania kliniczne opisano w artykule Burford i wsp. [76] oraz Gelinas i wsp. [73]. Podkreśla się potrzebę wdrażania dodatkowego przeglądu naukowego przeprowadzanego przez zewnętrzny zespół ekspertów w celu oceny protokołów badań. Przegląd protokołu powinien mieć miejsce przed rozpoczęciem

badania, a zespoły recenzentów powinny angażować ekspertów w dziedzinie statystyki i projektowania badań z dodatkową wiedzą specjalistyczną dostosowaną do rodzaju i fazy badania [76]. Po rozpoczęciu badania należy także monitorować dane z innych badań i na bieżąco weryfikować zasadność prowadzenia badania klinicznego [73].

W czasie pandemii COVID-19 w obliczu dużej liczby interwencji do zbadania dyskutowano na temat zasad ustalania priorytetów badawczych [59, 72]. Inną ważną kwestią był dynamiczny wzrost stosowania niepotwierdzonych interwencji klinicznych poza badaniami klinicznymi [54]. Wiele leków było przepisywanych we wskazaniach niezgodnych z przeznaczeniem, pomimo, że dowody na ich skuteczność w leczeniu i zapobieganiu COVID-19 były niewystarczające. To z kolei generowało potrzebę dostarczenia wysokiej jakości dowodów naukowych pozwalających na weryfikację, czy lek ma wartość terapeutyczną w danym wskazaniu [13]. Artkuł *„Ethical challenges of clinical trials with a repurposed drug in outbreaks”* (**P2**) przedstawia analizę etyczną, w której w oparciu o wytyczne zaproponowane przez Meyer i wsp. [41] starano się odpowiedzieć na pytanie czy zasadne było uruchomienie badań klinicznych nad amantadyną [2]. Analiza ta wskazuje, że presja społeczna i obawa przed dezinformacją mogą etycznie uzasadniać inicjację badań, nawet gdy podstawy naukowe są niewystarczające. Za takim rozwiązaniem przemawia m.in. analiza kosztu społecznego, polegającego na masowym stosowaniu substancji (w tym przypadku amantadyny) o niepotwierdzonej skuteczności do konkretnych wskazań, niezgodnych z przeznaczeniem leku (w tym przypadku COVID-19).

Pandemia COVID-19 była akceleratorem wielu zmian organizacyjnych i metodologicznych w obszarze badań klinicznych. Agencje regulacyjne i komisje bioetyczne próbowały usprawnić swoje procesy. Badania platformowe zyskały uwagę jako efektywny sposób generowania dowodów naukowych [25]. Znacząco wzrosła także liczba zdecentralizowanych badań klinicznych, czyli badań przeprowadzanych w całości lub w części poza tradycyjnymi ośrodkami badań klinicznych [77]. Pandemia COVID-19 przyspieszyła także wdrażanie zdalnych rozwiązań do prowadzenia i monitorowania badań klinicznych [25, 26]. Przeprowadzone analizy *„How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov”* (**P1**) i *„Ethical challenges of clinical trials with a repurposed drug in outbreaks”* (**P2**) dostarczają danych na temat wątpliwości etycznych, z jakimi wiązało się szybkie wdrażanie badań klinicznych w trakcie pandemii (szczególnie w jej początkowym okresie), a także ogólnej jakości i skuteczności tych badań w dostarczaniu istotnych informacji na temat leczenia i zapobiegania COVID-19.

Druga część rozprawy doktorskiej dotyczy etycznej analizy wybranych akceleratorów metodologicznych badań klinicznych prowadzonych w onkologii. W onkologii wykorzystuje się wiele innowacyjnych projektów badań klinicznych, których celem jest przyspieszenie rozwoju leków [10, 22, 23, 41]. W pewnym stopniu jest to uwarunkowane pilną potrzebą przyspieszenia zatwierdzania leków w celu poprawy leczenia i opieki onkologicznej. Co więcej, rozwój nowych terapii, wprowadzenie koncepcji medycyny precyzyjnej oraz rozwój narzędzi umożliwiających charakterystykę molekularną komórek nowotworowych i ich mikrośrodowiska sprawiły, że badania kliniczne w onkologii odchodzą od oceny leków cytotoksycznych na rzecz coraz większej liczby badań skupiających się na lekach ukierunkowanych molekularnie (co wiąże się z powszechniejszym zastosowaniem terapii celowanych i immunoterapii) [61]. To przyczyniło się do rozwoju nowych modeli badań klinicznych takich jak badania koszykowe, badania parasolowe lub badania platformowe [8, 78]. Tego typu projekty badań oferują różne zalety w porównaniu z tradycyjnymi modelami badań klinicznych m.in. testują wiele terapii, indywidualnie lub w kombinacji z innymi terapiami, i/lub wiele chorób równolegle w ramach jednego nadrzędnego protokołu. Przemawia to za efektywnością operacyjną, ponieważ ta sama infrastruktura jest opracowywana i wdrażana dla wielu ramion badania jednocześnie [8].

Badania kliniczne o modelu ciągłym, które umożliwiają płynne przejście między fazami rozwoju klinicznego również zyskują na popularności w obszarze onkologii. Wiele takich projektów jest szeroko stosowanych na wczesnym etapie opracowywania leków, co skutkuje badaniami klinicznymi fazy I lub fazy I/II, które pozwalają oszacować zarówno maksymalną tolerowaną dawkę, jak i skuteczność leczenia przy zastosowaniu tej dawki [19-21]. Niektóre badania kliniczne, w których wykorzystano ten model, doprowadziły do zatwierdzenia obiecujących leków przeciwnowotworowych w rekordowo krótkim czasie (było to dopuszczenie do obrotu w trybie procedury przyspieszonej). Warte uwagi przykłady to badanie kliniczne KEYNOTE-001 i CHECKMATE-040 [20]. Chociaż nowe model badawcze stają się coraz bardziej popularne i są powszechnie stosowane, nadal istnieje wiele wyzwań zarówno w projektowaniu, jak i przeprowadzaniu tych badań. Złożoność projektu może nasilać inne problemy w prowadzeniu badań klinicznych, również te z zakresu etyki badań [64].

Artykuł *„Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis”* (**P3**) to analiza wskaźników ryzyka i korzyści badań koszykowych w onkologii [3]. Badania koszykowe oceniają jedną lub więcej terapii, które mają działanie ukierunkowane na określone zmiany molekularne. Umożliwiają ocenę nowych metod leczenia w grupie uczestników

z różnymi typami nowotworów (niezależnie od lokalizacji), które charakteryzują się obecnością określonego biomarkera lub zmiany molekularnej [8, 61]. Zrównoważenie wskaźników korzyści i ryzyka stanowi główny element oceny podczas zatwierdzania nowych leków przez organy regulacyjne, a także podczas podejmowania decyzji terapeutycznych. W badaniu dokonano pomiaru wskaźników oceny ryzyka i korzyści, aby sprawdzić czy uczestnicy biorący udział badaniach koszykowych uzyskują korzystniejsze wskaźniki odpowiedzi niż w przypadku innych typów badań klinicznych. Oczekuje się, że badania kliniczne koszykowe będą miały wyższy wskaźnik odpowiedzi na leczenie niż standardowe projekty testujące interwencje na podstawie umiejscowienia nowotworu. Jednak zebrane dane nie wspierają tej hipotezy. W publikacji porównano uzyskane wskaźniki ryzyka i korzyści dla badań koszykowych z dostępnymi danymi na temat ryzyka i korzyści w innych typach badań w onkologii, odnosząc się m.in. do wskaźników ryzyka i korzyści dla badań fazy I [79, 80], badań fazy II [81], oraz badań parasolowych [37]. Na przykład, odsetek obiektywnych odpowiedzi – ORR (a więc odsetek uczestników badania, u których zaobserwowano częściową lub całkowitą regresję nowotworu) – dla badań koszykowych fazy II wynosił 15,1% (95% CI 11,6–18,6). Wynik ten jest podobny do ORR wynoszącego 14,0% (95% CI 6,9–21,2) w badaniach parasolowych fazy II [37], a także podobny do wskaźnika odpowiedzi w standardowych badaniach testujących pojedynczą interwencję, dla których ORR wynosił 12,7% (95% CI 11,6–13,9) [81]. Uzyskane wyniki stanowią empiryczną podstawę do informowania o wskaźnikach ryzyka i korzyści dla koszykowych badań klinicznych, również w odniesieniu do innych modeli badawczych.

Transparentne i pełne raportowanie metod i wyników wszystkich badań klinicznych jest uznane za etyczny i naukowy wymóg mający na celu promowanie kompletnej bazy dowodowej i ograniczenie marnotrawstwa badawczego. Jest to także narzędzie zwiększające wartość badań klinicznych oraz sposób na budowanie publicznego zaufania do przedsięwzięć badawczych [5, 82]. Jeśli wyniki badania nie zostaną upublicznione, inwestycja w zasoby i wysiłek włożony w jego prowadzenie zostaną zmarnowane. Terminowe udostępnianie wyników badań ma kluczowe znaczenie dla kształtowania przyszłych badań, ograniczenia zbędnego powielania badań i umożliwienia prowadzenia opieki w oparciu o aktualną wiedzę [5]. Konieczność terminowego, kompletnego i dokładnego raportowania wyników została podkreślona w najnowszej wersji Deklaracji Helsińskiej z 2024 r. [66] oraz w wytycznych WHO z 2024 r. dotyczących najlepszych praktyk w zakresie badań klinicznych [82]. Coraz większy nacisk kładzie się na udostępnianie wyników w rejestrach badań klinicznych, które w przypadku braku publikacji w postaci artykułu naukowego są jedynym źródłem informacji o badaniu. W artykule opublikowanym w kwietniu

2025 roku na łamach czasopisma *The Lancet Global Health* przedstawiono wytyczne WHO dotyczące raportowania wyników w rejestrach badań klinicznych, tak aby ujednolicić sposób prezentacji wyników pomiędzy różnymi rejestrami badań klinicznych [82]. Wskazano na niezbędne elementy, które powinny być uwzględnione w strukturze rejestrów badań klinicznych, by w przejrzysty sposób prezentować wyniki i opis badania.

Problem raportowania wyników badań został poruszony zarówno w publikacji *„Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis"* (**P3**) [3], jak i w publikacji *„Seamless trials in oncology: A cross-sectional analysis of characteristics and reporting"* (**P4**) [4]. W publikacji **P3** zwrócono uwagę na selektywne raportowanie wyników dla poszczególnych punktów końcowych. Niektóre dane były łatwo dostępne w analizowanych publikacjach i podsumowaniu wyników dostępnym w rejestrze ClincialTrials.gov, podczas gdy inne były bardzo ograniczone. Przykładowo, dane na temat ORR były dostępne w przypadku 83.3% badań, a dane na temat śmiertelności związanej z leczeniem tylko w przypadku 44.4%. W publikacji *„Seamless trials in oncology: A cross-sectional analysis of characteristics and reporting"* (**P4**) przedstawiono dowody na niski stopień raportowania wyników badań o modelu ciągłym stosowanych we wczesnej fazie rozwoju leków onkologicznych. Choć niska dostępność wyników w rejestrach jest powszechnie znana i uzyskany wynik nie był zaskakujący, w publikacji **P4** wskazano na potrzebę dostosowania sposobu prezentacji wyników oraz opisu projektu badania w rejestrze *ClinicalTrials.gov* do nowych modeli badawczych. Problem ten został także poruszony przez innych autorów w kontekście badań, które mają złożone protokoły badawcze tzn. są badaniami wieloramiennymi i wieloetapowymi – ich przykładem są m.in. badania platformowe, koszykowe czy parasolowe [83]. Uzyskane dane wspierają postulaty dotyczące konieczności dostosowania systemów służących do rejestracji i raportowania wyników badań do ciągłych zmian jakie zachodzą w projektowaniu i prowadzeniu badań klinicznych.

6.6 Wnioski

Badania kliniczne nieustannie ewoluują. Rozważając przyspieszenie badań klinicznych należy uwzględnić szereg kwestii organizacyjnych oraz zmian regulatorowych, które są konieczne do wprowadzenia zmian. Jednocześnie nie należy zapominać o kwestiach etycznych tych badań. Zasady etyczne chronią uczestników badań, a także zapewniają wysoką jakość dostarczanych danych, przeciwdziałając tym samym marnotrawstwu badawczemu i narażeniu uczestników na niepotrzebne ryzyko.

W rozprawie doktorskiej na podstawie wybranych przykładów omówione zostały zagadnienia etyczne związane z akceleracją badań klinicznych. Pierwszą część pracy stanowią dwie analizy dotyczące badań klinicznych rozpoczętych w czasie pandemii COVID-19. Na podstawie przeprowadzonych analiz udowodniono, że znaczna część badań uruchomionych w początkowej fazie pandemii była źle zaprojektowana pod kątem jakości projektu badawczego, wykonalności rekrutacji i oryginalności testowanej hipotezy badawczej. W jednej pracy wykazano, że blisko 70% badań nie spełniało kryteriów informatywności badań klinicznych, co oznacza, że badania te choć zainicjowane bardzo szybko, miały małe szanse na dostarczenie wysokiej jakości dowodów naukowych przyczyniając się do marnotrawstwa badawczego. W drugiej pracy przedstawiono analizę zasadności uruchomienia badań klinicznych nad amantadyną, która w Polsce wzbudziła podczas pandemii ogromne zainteresowanie jako potencjalny środek terapeutyczny. Wykazano, że w niektórych przypadkach, mimo niskiej jakości dowodów wspierających testowanie hipotezy badawczej, koszt społeczny nieuruchomienia badania klinicznego może być zbyt duży. Argument ten nie może być jednak wykorzystywany jako usprawiedliwienie złego planowania badań. W takich sytuacjach konieczna jest współpraca pomiędzy badaczami, aby możliwe było szybkie zebranie wysokiej jakości dowodów naukowych oraz konsolidacja wysiłków, aby uniknąć marnotrawstwa badawczego i prowadzenia wielu badań testujących podobne (lub nawet te same) hipotezy badawcze.

W drugiej części rozprawy doktorskiej uwagę poświęcono nowym modelom badań klinicznych w onkologii, które wykorzystują akceleracje metodologiczne. Z jednej strony analizowano dane na temat ryzyka i korzyści badań koszykowych w onkologii. Takie analizy prowadzone w oparciu o techniki metabadawcze dostarczają danych na temat wskaźników odpowiedzi oraz odsetka uczestników, którzy doświadczają ciężkich (w tym tych śmiertelnych) działań niepożądanych związanych z leczeniem. Wyniki te mają duże znaczenie dla informowania przyszłych

uczestników badań koszykowych, a także oceny efektywności wdrażania nowych rozwiązań w badaniach klinicznych przez sponsorów badań czy organizacje regulatorowe.

W drugiej publikacji uwagę poświęcono raportowaniu tzw. ciągłych badań klinicznych stosowanych we wczesnej fazie rozwoju leków. Wykazano, że wyniki tych badań są w niskim stopniu raportowane w rejestrze *ClinicalTrials.gov* (opublikowane wyniki posiadało zaledwie 34,7% spośród analizowanych badań). Dodatkowo udowodniono, że wraz z pojawieniem się nowych modeli badawczych konieczne jest dostosowanie istniejących narzędzi, które służą do rejestrowania czy raportowania wyników badań klinicznych. Badania te często mają złożoną strukturę, dlatego konieczne jest bieżące aktualizowanie istniejącej infrastruktury tak, aby możliwe było transparentne prezentowanie metodyki badania i w późniejszej fazie ich wyników. Rola rejestrów takich jak *ClinicalTrials.gov* jest ogromna. Często jest to pierwsze źródło informacji o badaniu skierowane do szerszego grona – zarówno pacjentów, którzy mogą stać się uczestnikami, jak innych jednostek prowadzących badania kliniczne. Dlatego istotne jest, aby dostępne tam dane były spójne i przedstawione w sposób przystępny, nawet jeśli model badania klinicznego jest złożony.

Cykl publikacji przedstawiony w niniejszej dysertacji pokazuje, że organizacyjne i metodologiczne formy akceleracji prowadzenia badań klinicznych powinny wiązać się ze ścisłym nadzorem i kontrolą takich przedsięwzięć. Pozwoli to na ciągłe udoskonalanie rozwiązań i utrzymanie bezpieczeństwa uczestników na wysokim poziomie.

7 Publikacje

7.1 Publikacja P1

PLOS ONE

RESEARCH ARTICLE

How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov

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Abstract

Background

Early in the SARS-CoV-2 pandemic, commentators warned that some COVID trials were inadequately conceived, designed and reported. Here, we retrospectively assess the prevalence of informative COVID trials launched in the first 6 months of the pandemic.

Methods

Based on prespecified eligibility criteria, we created a cohort of Phase 1/2, Phase 2, Phase 2/3 and Phase 3 SARS-CoV-2 treatment and prevention efficacy trials that were initiated from 2020-01-01 to 2020-06-30 using ClinicalTrials.gov registration records. We excluded trials evaluating behavioural interventions and natural products, which are not regulated by the U.S. Food and Drug Administration (FDA). We evaluated trials on 3 criteria of informativeness: potential redundancy (comparing trial phase, type, patient-participant characteristics, treatment regimen, comparator arms and primary outcome), trials design (according to the recommendations set-out in the May 2020 FDA guidance document on SARS-CoV-2 treatment and prevention trials) and feasibility of patient-participant recruitment (based on timeliness and success of recruitment).

Results

We included all 500 eligible trials in our cohort, 58% of which were Phase 2 and 84.8% were directed towards the treatment of SARS-CoV-2. Close to one third of trials met all three criteria and were deemed informative (29.9% (95% Confidence Interval 23.7–36.9)). The proportion of potentially redundant trials in our cohort was 4.1%. Over half of the trials in our cohort (56.2%) did not meet our criteria for high quality trial design. The proportion of trials with infeasible patient-participant recruitment was 22.6%.

are available in the Open Science Framework repository, https://osf.io/fp726/.

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Conclusions

Less than one third of COVID-19 trials registered on ClinicalTrials.gov during the first six months met all three criteria for informativeness. Shortcomings in trial design, recruitment feasibility and redundancy reflect longstanding weaknesses in the clinical research enterprise that were likely amplified by the exceptional circumstances of a pandemic.

Introduction

Starting in early 2020, commentators warned of COVID-19 clinical trial design deficiencies and lack of coordination of research efforts [1–4]. The large volume of small trials investigating the efficacy of repurposed medications, such as hydroxychloroquine, in the treatment of COVID-19, drew particular attention [5,6]. Such studies confounded an effective public health response by producing spurious findings, or by diverting patients and resources from well designed and executed studies.

Appropriate design, implementation and reporting is captured by the concept of trial "informativeness" [3,7]. For a trial to be informative to clinical practice, it must fulfill five conditions [3,7]. First, it must ask a clinically important question. Second, it must be designed to provide a clear answer to that question. Third, it must have both a feasible enrollment target and primary completion timeline. Fourth, it must be analyzed in a manner that supports statistically valid inference. Fifth, it must report results in a complete and timely manner [3,7].

In the following longitudinal cohort analysis of SARS-CoV-2 treatment and prevention trials registered within the first 6 months of 2020, we assess three features of an informative clinical trial—potential redundancy, design quality and feasibility of patient-participant recruitment. Multiple cross-sectional analyses and systematic reviews of SARS-CoV-2 treatment and prevention trials have been performed [2,5,6,8–11], reporting on intervention types, study characteristics and choice of outcome measure. We go beyond a description of trial characteristics and provide the first in-depth evaluation of SARS-CoV-2 trial informativeness. Knowing the prevalence of potentially uninformative trials conducted in the early stages of the pandemic can help motivate the development of more effective research policy in anticipation of future public health crises.

Methods

Sample, design and trials selection

Our cohort consisted of interventional SARS-CoV-2 treatment and prevention trials registered on ClinicalTrials.gov with a start date between 2020-01-01 and 2020-06-30. We included "Completed", "Terminated", "Suspended", "Active, not recruiting", "Enrolling by invitation" and "Recruiting" Phase 1/2, Phase 2, Phase 2/3 and Phase 3 interventional clinical trials testing an efficacy hypothesis in their primary outcome. We included trials evaluating any of the following interventions: drug, biological, surgical, radiotherapy, procedural or device. We excluded trials evaluating behavioural interventions, trials of natural products and Phase 1 trials, all of which have no legal requirement to register on ClinicalTrials.gov [12]. See S1 File for complete inclusion/exclusion criteria. Trial inclusion and exclusion criteria were independently assessed by two researchers (KK & LZ), with disagreements resolved by an arbiter (NH or MW). We did not perform a sample size calculation, as we included all trials meeting our eligibility criteria within our designated sampling timeframe.

Data curation

We downloaded clinical trial data directly as a zipped folder of XML files from the web front-end of ClinicalTrials.gov on 2020-12-01 and again on 2021-01-04 (see S2 File for ClinicalTrials.gov search criteria). This allowed us to evaluate data at the 6-month mark (from date of trial start) for all trials in our cohort (see S3 File for data directly downloaded from ClinicalTrials.gov). Additional items requiring human curation were independently assessed and coded by two researchers (KK & LZ), these included: i) treatment type (according to the World Health Organization (WHO) COVID-19 Classification of treatment types [13]); ii) illness severity (as stated by the study investigators or guided by the WHO disease severity classification [14]); iii) location of care (ambulatory, hospitalized, intensive care, unclear/not stated); iv) presence of a placebo or standard of care arm; and, v) type of primary outcome (clinical, surrogate, procedural) (see S4 File for additional double-coded data points). Disagreements were resolved by an arbiter (NH or MW) (Please see S1 Table for inter-rater agreement).

Measures

Trials were assessed based on three elements of informativeness: i) potential redundancy (as a marker of trial importance); ii) trial design quality; and iii) successful patient-participant recruitment (as a marker of feasibility). Assessment criteria for each element were designed based on face validity and easy applicability over a large trial sample.

Potential redundancy. We assessed potential redundancy by evaluating non-redundancy of the trial hypothesis. Non-redundancy was defined as: absence of a trial of the same phase, type of trial (SARS-CoV-2 prevention versus treatment), patient-participant characteristics (including location of care, disease severity and age of trial participants), regimen (including interventions used in combination in a single arm), comparator arm(s) and primary outcome (evaluating primary outcome domain and specific measurement, based on framework from [15]) launched prior to the start date of the trial of interest (as indicated in the registration record active at the 6-month mark since trial start) (S5 File). Only the trial with the later start date was labelled as potentially redundant. The assessment was independently performed by two raters (NH & KK), with disagreements resolved by an arbiter (MW of BC). We performed an additional *post hoc* assessment applying a broad criterion for trial similarity, which we defined as presence of a trial with an earlier start date of the same type, phase, patient-participant characteristics and treatment regimen.

Design quality. We analyzed trial design quality for those studies in our sample that were aimed at informing clinical practice–namely Phase 2/3 and Phase 3 trials. Based on the U.S. Food & Drug Association (FDA) May 2020 guidance document for SARS-CoV-2 drug and biological treatment and prevention trials [16], we considered a trial to be well-designed if it was randomized, placebo-controlled or with a standard of care comparator arm, double-blinded and included participants aged 60 years or over (as a proxy for an at-risk population). To be considered well-designed, a trial must also measure an appropriate primary outcome–a clinical primary outcome in the case of trials aimed at treating COVID-19, or the presence of laboratory-confirmed SARS-CoV-2 infection for trials testing a preventive measure.

Feasibility of patient-participant recruitment. We assessed timeliness and success of patient-participant recruitment for each trial in our cohort. A single trial was considered non-feasible if it met any of the following criteria: i) trial status was "terminated" or "suspended" and reason for stopping contained a rationale unrelated to trial efficacy, safety or the progression of science; ii) trial status was "completed" or "active, not recruiting" and final enrollment was less than 85% of the anticipated enrollment reported in the trial registration at the time of

trial launch (given concerns for compromised statistical power for the primary outcome when recruitment is below the stated threshold (based on previously published methods [17]); or, iii) trial status was "recruiting" or "enrolling by invitation" and the recruitment period had been extended to at least twice as long as the anticipated length in the version of ClinicalTrials.gov registration record at the time of trial start.

Data analysis

We report the overall proportion of trials meeting all three criteria of informativeness (potential redundancy, design quality and feasibility of patient-participant recruitment) as well as the proportion meeting each of our three criteria. We performed a stratified analysis of the proportion of i) non-redundant; ii) well-designed; and iii) feasible trials by sponsor (industry versus non-industry), trial country location (USA versus non-USA), trial type (treatment versus prevention) and number of trial centers (single center versus multicenter). Ninety-five percent confidence intervals were calculated for the difference between two proportions using the prop.test package in R [18]. All tests were 2-tailed. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies (S1 Checklist) [19].

Tools and data synthesis

We performed data extraction using Numbat Systematic Review Manager v. 2.11 (RRID: SCR_019207) [20]. All analyses were performed using R version 3.6.3 [21]. We retrieved historical versions of ClinicalTrials.gov using R package 'cthist' (RRID:SCR_019229).

Our study was not subject to Institutional Review Board/Ethics Committee approval, as it relies on publicly accessible data and did not involve interaction with research participants. The study protocol was prospectively registered on Open Science Framework [22]. We listed the deviations from the protocol in S6 File. The code [23] and data sets [22] used in this analysis are available online.

Results

We included 500 interventional SARS-CoV-2 treatment and prevention efficacy trials (see S1 Fig for Flow Diagram). The number of trials was arrived at by chance and was not predetermined. The majority (58.0%) of trials in our cohort were Phase 2 trials; 84.6% were randomized; 84.8% were directed at the treatment of SARS-CoV-2. Study status at 6 months since trial start was "Completed" in 54 of 500 trials (10.8%) and "Recruiting" in 67.0% (Tables 1, S2 and S3). Median anticipated enrollment per trial (based on the enrollment stated in the last registration record prior to trial start) was 180 patient-participants (range 5–15000 patient-participants; interquartile range (IQR) 60–437). Median actual patient-participant enrollment at the 6-month mark, for those trials that provided actual enrollment numbers, was 129 (range 0–4891 patient-participants; IQR 32–320).

Less than one third (29.9%, 95% CI 23.7–36.9%) of the 194 trials eligible for assessment of all 3 criteria were deemed informative. Nineteen trials were classified as potentially redundant (4.1%), of which 10 investigated convalescent plasma and a further 4 investigated hydroxychloroquine. Sixty-three trials (13.6%) differed only by primary outcome. In our *post hoc* analysis, 81.9% (380 of 464 trials) were similar with respect to trial type, regimen, phase and patient-participant characteristics.

Of the subset of 210 Phase 2/3 and Phase 3 trials in our cohort, 92 (43.8%) met our criteria for trial design quality [20] (Fig 1; Table 2). The proportion of feasible trials in our cohort was 77.4% (387 of 500 trials); 113 trials were non-feasible. Of these, 12 were "Suspended" or

Table 1. Characteristics of trial cohort.

Category	Number of Trials (N = 500)	Percent Total (%)	Median (IQR) Anticipated Enrollment[a]	Median (IQR) Actual Enrollment[b]
Trial Phase				
Phase 1/2 & Phase 2	290	58.0	100 (40–200)	60 (25–152)
Phase 2/3 & Phase 3	210	42.0	400 (183–1000)	241 (95–494)
Randomization				
Randomized	423	84.6	200 (82–482)	142 (53–357)
Non-Randomized	30	6.0	73 (30–248)	38 (20–102)
NA[c]	47	9.4	37 (20–100)	27 (10–50)
Trial Status[d]				
Completed	54	10.8	100 (46–396)	100 (40–387)
Terminated	16	3.2	265 (150–464)	62 (7–127)
Active, Not Recruiting	71	14.2	240 (68–500)	177 (55–442)
Recruiting	335	67.0	152 (60–410)	143 (26–230)
Enrolling by Invitation	11	2.2	128 (56–400)	72 (51–152)
Suspended	13	2.6	308 (200–600)	27 (5–71)
Trial Type				
Treatment Trial	424	84.8	130 (60–333)	100 (30–233)
Prevention Trial	66	13.2	672 (206–1729)	554 (75–1346)
Treatment & Prevention	10	2.0	782 (250–1500)	741 (166–1557)
Sponsorship				
Industry Sponsor	112	22.4	195 (82–400)	187 (84–413)
Non-Industry Sponsor	388	77.6	177 (60–455)	100 (27–269)
Country Location				
USA Trial	179	35.8	200 (60–460)	95 (24–243)
Non-USA Trial	321	64.2	165 (60–426)	121 (39–324)
Number of Centers				
Single Center	198	39.6	100 (37–290)	60 (20–213)
Multicenter	302	60.4	226 (100–500)	143 (53–401)

a) Anticipated enrollment in the first registration record after trial start.

b) At the 6-month mark, for the subset of trials which provide actual enrollment information.

c) NA–Information not available in the ClinicalTrials.gov registration record.

d) Trial Status at the 6-month mark since trial start.

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"Terminated "for a reason unrelated to efficacy, safety or the progression of science; 20 trials were "Active, not recruiting" or completed but failed to enrol at least 85% of their target patient-participant enrollment (S2 Fig); 81 trials still "Recruiting" had exceeded at least two times the intended recruitment period (S3 Fig).

Discussion

Prior studies have examined the COVID-19 trial landscape, evaluating trial design quality [24,25], choice of outcome [26], and presenting descriptive statistics on COVID-19 trials characteristics [2,5,6,8–11]. This is the first study to assess the prevalence of informative COVID-19 clinical trials. In our analysis, 29.9% of early COVID-19 trials registered on ClinicalTrials.gov met our 3 criteria for informativeness. Many (56.2%) did not use rigorous design, based on assessment of randomization, control group, blinding, primary outcome, and inclusion of an at-risk population. Of these, the greatest number (110 of 210 trials, 52.4%) did not demonstrate adequate blinding. Lack of blinding among COVID-19 trials has been highlighted in

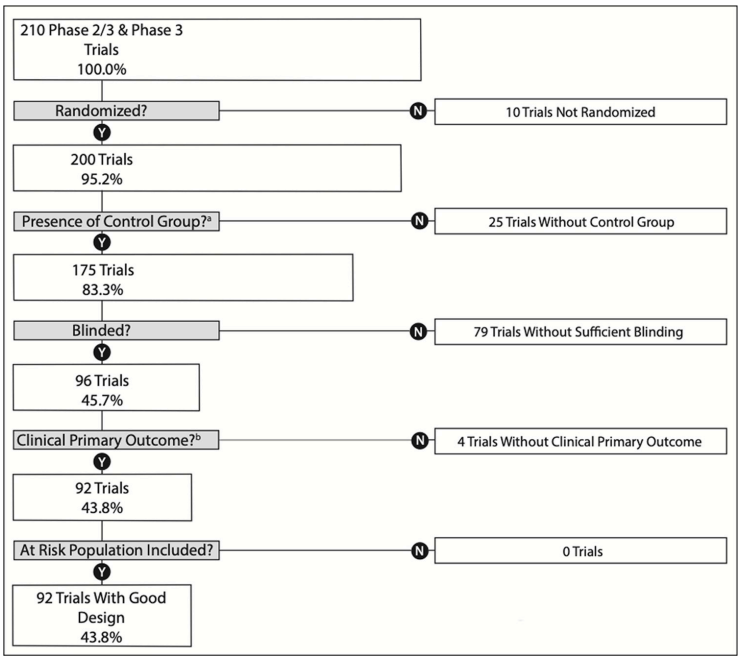

Fig 1. Flow diagram for trial design quality of Phase 2/3 and Phase 3 SARS-CoV-2 trials. a) Refers to trial that is either placebo-controlled or has a standard of care comparator arm. b) Refers to a treatment trial with a clinical primary outcome or a prevention trial with either a clinical primary outcome or laboratory-confirmed SARS-CoV-2.

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several recent analyses [2,5,6,9,10] and may reflect the challenges of trial conduct in pandemic circumstances, in which significant research infrastructure and oversight is required to implement and maintain blinding. Yet, deficits in trial design were not uniform. Our stratified results (Table 3) demonstrated that trials with at least one center in the USA, in addition to

Table 2. Evaluation of design quality of trials meant to inform clinical practice.

Category	Number of Trials (N = 210)	Percent Total (%)
Randomized	200	95.2
Placebo-Controlled	179	85.2
Blinded[a]	100	47.6
Clinical Primary Outcome[b]	203	96.7
Includes at Risk Population[c]	208	99.0
Trials Meeting all 5 Criteria	**92**	**43.8**

a) Refers to trials that were at a minimum double-blinded.

b) Treatment trials required a primary clinical outcome; prevention trials required either a primary clinical outcome or laboratory-confirmed SARS-CoV-2.

c) We defined an at risk population as a trial including participants aged $\geq$ 60.

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Table 3. Stratified analysis of redundancy, design, trial feasibility and informativeness by sponsor, country location, trial type, number of trial centers.

Informative Condition	Yes (%)	No (%)	| Difference | (95% CI)
Non-Redundant			
Industry Sponsored	99.1	94.9	4.1 (0.6–7.6)
USA Trial	95.8	96.0	0.2 (-3.8–4.2)
Treatment Trial	95.9	95.5	0.4 (-5.4–6.3)
Multicenter Trial	94.7	97.8	3.1 (-0.8–6.9)
Good Design			
Industry Sponsored	73.9	35.4	38.5 (22.5–54.6)
USA Trial	72.4	32.9	39.5 (24.6–54.4)
Treatment Trial	39.2	62.9	23.7 (4.4–43.0)
Multicenter Trial	48.7	31.0	17.6 (2.1–33.2)
Feasible			
Industry Sponsored	71.4	79.1	7.7 (-2.2–17.6)
USA Trial	69.8	81.6	11.8 (3.4–20.2)
Treatment Trial	78.3	71.2	7.1 (-5.4–19.6)
Multicenter Trial	73.2	83.8	10.7 (3.1–18.2)
Informative[a]			
Industry Sponsored	52.2	23.0	29.2 (11.8–46.6)
USA Trial	40.7	25.7	15.0 (-1.2–31.3)
Treatment Trial	28.4	31.4	3.0 (-15.6–21.7)
Multicenter Trial	30.1	29.2	1.0 (-14.9–16.8)

a) Informative trials are those that meet all 3 informativeness criteria.

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trials with industry sponsorship, SARS-CoV-2 prevention trials and multicenter trials, demonstrated a greater proportion of well-designed trials than their counterparts.

Despite elevated SARS-CoV-2 cases, many trials (22.6% (113 of 500 trials)) were unable to adequately and expeditiously complete patient-participant recruitment. This estimate is in keeping with other studies in which close to one third of COVID-19 trials registered on ClinicalTrials.gov or on the World Health Organization International Clinical Trials Registry Platform stopped before attaining 75% accrual [27]. In some cases failure to reach recruitment goals can be explained by decreasing case counts in the setting of rapid suppression of a COVID outbreak. For example, early stoppage of a Remdesivir multicenter randomized controlled trial after recruitment of 237 of 453 patient-participants in Wuhan, China, resulted in an underpowered trial with inconclusive results [28,29]. This has also been seen in other settings, such as in the 2014–2016 Ebola outbreak [30]. However, infeasible recruitment targets, despite high case counts, have also been documented during the COVID-19 pandemic [31]. Trial feasibility may be particularly challenging in the fractured US healthcare setting due to inter-trial competition in patient-participant recruitment, as supported by our stratified analysis in which non-USA trials were significantly more likely to be feasible than USA trials.

Lack of coordination and trial prioritization, resulting in a high level of multiplicity in investigated interventions, is a contributing factor to infeasible patient-participant recruitment. Concern about trial redundancy has been brought up frequently during the COVID-19 pandemic [1,2,4,5]. In our study, only 4.1% of trials were deemed potentially redundant, of which 4 investigated hydroxychloroquine and 10 investigated the efficacy of convalescent plasma. Our categorization of trials as potentially redundant involved matching of trial phase, type of trial (treatment versus prevention), patient-participant characteristics, regimen,

comparator and primary outcome. It differs from other assessments of SARS-CoV-2 trial duplication, in which trial intervention has been the main focus of assessment [2]. While a low proportion of potentially redundant trials may be seen as an encouraging result, deeper examination reveals that sixty-three trials (13.6%) assessed for potential redundancy differed only by the choice of primary outcome, with endpoints often demonstrating small deviations from comparator trials, of questionable clinical relevance. For instance, some trials expressed the primary endpoint as a function of time e.g., time to death, whereas in others as a rate e.g., case fatality rate. Our *post hoc* analysis of trial similarity, which evaluated trial type, regimen, phase and patient-participant characteristics, revealed that 81.9% of trials were similar, reflecting the extent to which early clinical trials during the COVID-19 pandemic pursued comparable study designs.

Replication in research is important to clarify study results. However, lack of research coordination and harmonization of primary outcome endpoints during the COVID-19 pandemic [2,4,32,33] can thwart efforts to clarify net effects through meta-analyses. This is particularly relevant in the setting of multiple small trials of specific interventions, where the probability is elevated that at least one trial produces a positive result by chance alone [2,5]. Prospective meta-analyses (PMA), which encourage harmonization of core outcomes and draw on individual participant data, can help clarify treatment effects and reduce research waste [34]. In this way, individually underpowered studies can help address questions of significant clinical importance. Although successfully employed in other medical settings [35,36], PMAs were unfortunately not widely deployed in the early COVID-19 pandemic.

Concerns regarding research waste predated the pandemic [37–43] but intensified in the setting of this international public health crisis. Our results support arguments for devising coordinated research plans in advance of public health emergencies [44], and evaluating and prioritizing trials at institutional [45,46], state and national levels [47]. The success of multicenter national platform trials, such as RECOVERY, in the United Kingdom, in both recruiting patient-participants (over 45580 have been enrolled as of December 9 2021, https://www.recoverytrial.net) and in generating practice-changing evidence, speaks to the promise of national research prioritization [48]. Additional strategies to improve pandemic preparedness include: i) promotion of individual participant data sharing platforms to capitalize on data generated, even from small trials [49]; ii) prioritization of adaptive master protocol trials investigating promising interventions [44,49]; and, iii) increased research collaboration, in the model of the Coalition for Epidemic Preparedness Innovations (CEPI). In our stratified analysis, industry-sponsored trials were significantly more likely to meet all 3 informativeness criteria than non-industry sponsored trials (Table 3). This suggests that academic researchers require more institutional support, as well as assistance from research consortia and funding bodies to produce informative results.

Limitations

First, we limited our assessment to 3 aspects of trial informativeness–potential redundancy, design quality and feasibility of patient-participant recruitment. Other aspects of informativeness, such as integrity and reporting, were not evaluated in our study, as they cannot be assessed without access to final trial results (430 of 500 trials, 86.0% had not yet completed or terminated at the end of our 6-month follow-up period). A follow-up study evaluating data 24 months after trial launch would enable a comprehensive assessment of trial informativeness, and thus represents an area for future research. Second, we used proxy measures of informativeness, which are imperfect. For example, we adopted strict criteria for potential redundancy, resulting in only 19 trials labelled potentially redundant, many of which differed based on

primary outcome alone. Our *post hoc* analysis resulted in over eighty percent of trials deemed similar, based on assessment of trial type, regimen, phase and patient-participant characteristics. These two results (4.1% and 81.9%) can be viewed as lower and upper bounds for the proportion of redundant trials. Missing from our assessment was an evaluation of the availability and quality (as assessed by GRADE [50]) of pre-existent evidence of intervention efficacy which may render subsequent trials redundant. We also did not assess the extent to which individual participant data were made publicly available (for example, through the Vivli platform [51]), and subsequently incorporated into meta-analyses. Our redundancy evaluation should thus be interpreted with caution and future research will be required to provide a more precise estimate. Our assessment of trial design quality, as guided by the May 2020 FDA guidance document [16], required that all trials be, at a minimum, double-blinded. We acknowledge that this may unfairly penalize the small minority of trials evaluating interventions in which double-blinding is not practicable. In addition, our assessment of the inclusion of at-risk populations was limited only to age. We did not assess whether the study included a population with other risk factors such as comorbidities. However, no trials failed our design criteria based on failure to include an at-risk population. Third, our assessment of the informativeness of COVID-19 trials depends on the accuracy of ClinicalTrials.gov registration records. Fourth, our findings may not be generalizable to all COVID-19 interventional clinical trials. For example, public health behavioural interventions are frequently labelled as "Phase NA" and would therefore not be included in our findings.

Conclusions

The SARS-CoV-2 pandemic was met with a vigorous response from clinical researchers. However, less than one third of early COVID-19 trials registered on ClinicalTrials.gov met our 3 criteria for informativeness. Shortcomings in trial design, recruitment feasibility and redundancy reflect longstanding vulnerabilities in the clinical research enterprise that were magnified by the urgency of a pandemic. Much knowledge has been gained since the first six months of the COVID-19 pandemic, both in terms of effective measures aimed at treatment and prevention of the virus, but also with respect to the conduct of informative clinical research. The task ahead will be for investigators, research institutions, sponsors and regulators alike to take stock of lessons learned and devise solutions to benefit the global research enterprise as we move forward.

Supporting information

S1 Checklist. STROBE statement—Checklist of items that should be included in reports of *cohort studies*.
(DOCX)

S1 Fig. Flow diagram of trial inclusion/exclusion.
(DOCX)

S2 Fig. Ratio of actual to estimated number of patients enrolled.
(DOCX)

S3 Fig. Ratio of actual to estimated recruitment length.
(DOCX)

S1 Table. Inter-rater agreement.
(DOCX)

S2 Table. Additional characteristics of trial cohort.
(DOCX)

S3 Table. Range of anticipated and actual enrollment.
(DOCX)

S1 File. Trial inclusion and exclusion criteria.
(DOCX)

S2 File. ClinicalTrials.gov search criteria.
(DOCX)

S3 File. Data downloaded from ClinicalTrials.gov.
(DOCX)

S4 File. Additional data points.
(DOCX)

S5 File. Assessment of trial redundancy.
(DOCX)

S6 File. Protocol deviations.
(DOCX)

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7.2 Publikacja P2

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SCIENTIFIC CONTRIBUTION

Ethical challenges of clinical trials with a repurposed drug in outbreaks

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Abstract
Drug repurposing is a strategy of identifying new potential uses for already existing drugs. Many researchers adopted this method to identify treatment or prevention during the COVID-19 pandemic. However, despite the considerable number of repurposed drugs that were evaluated, only some of them were labeled for new indications. In this article, we present the case of amantadine, a drug commonly used in neurology that attracted new attention during the COVID-19 outbreak. This example illustrates some of the ethical challenges associated with the launch of clinical trials to evaluate already approved drugs. In our discussion, we follow the ethics framework for prioritization of COVID-19 clinical trials proposed by Michelle N Meyer and colleagues (2021). We focus on four criteria: social value, scientific validity, feasibility, and consolidation/collaboration. We claim that launching amantadine trials was ethically justified. Although the scientific value was anticipated to be low, unusually, the social value was expected to be high. This was because of significant social interest in the drug. In our view, this strongly supports the need for evidence to justify why the drug should not be prescribed or privately accessed by interested parties. Otherwise, a lack of evidence-based argument could enhance its uncontrolled use. With this paper, we join the discussion on the lessons learned from the pandemic. Our findings will help to improve future efforts to decide on the launch of clinical trials on approved drugs when dealing with the widespread off-label use of the drug.

Keywords Drug repurposing · Clinical trials · Amantadine · COVID-19 · Bioethics

Introduction

Drug repurposing, also known as drug repositioning or drug re-profiling, is a strategy of identifying new potential uses for existing drugs (Pushpakom et al. 2019; Parvathaneni et al. 2019; Ashburn and Thor 2004). Researchers can apply this method at any stage of the drug development process: from a substance at the preclinical level to the drug with authorization approval (Begley et al. 2021). Compared to the classical drug development pathway starting from the discovery of novel compounds, drug repurposing may accelerate the research process. This is because data collected for previously evaluated indications can be used as a basis for research on new efficacy assessment. Consequently, during repurposing some of the initial steps of drug development can be bypassed (Parvathaneni et al. 2019; Ashburn and Thor 2004).

The global outbreak of COVID-19 created unprecedented pressure on clinical trial regulators, ethics committees, researchers, and other stakeholders to develop prevention and treatment as quickly as possible. Various methods were adopted to speed up the delivery of data and verify the research hypothesis (Park et al. 2021). Many researchers turned to the existing drugs, which made drug repurposing a widely applied approach (Sahoo et al. 2021; Riva et al. 2020; Bakowski et al. 2021; Galindez et al. 2021; Venkatesan 2021). However, the urge to do "something" to help save patients with COVID-19 led to many poorly planned actions (Lynch et al. 2021). Many clinical trials testing the same drugs were conducted almost simultaneously, raising concerns about redundancy and waste (Lynch et al. 2021; Meyer et al. 2021; Hutchinson, Klas, Carlisle, Kimmelman, et al. 2022; Maziarz and Stencel 2022). These challenges reinforced the role of informative and ethical clinical research (Meyer et al. 2021; Hutchinson, Klas, Carlisle,

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Kimmelman, et al. 2022; London and Kimmelman 2020). Numerous guidelines and ethical frameworks were proposed to prevent research waste or misconduct and support clinical research during the COVID-19 pandemic (Hsu et al. 2021; London and Kimmelman 2020; Meyer et al. 2021).

This paper presents the case study of amantadine repurposing during the COVID-19 pandemic. This example illustrates some of the ethical challenges associated with the launch of clinical trials to evaluate already approved drugs. We discuss whether clinical trials of amantadine during the COVID-19 pandemic were ethically justified and should have been initiated. We focus on the impact of high social pressure on rapid clinical testing and the need for evidence, as it was during the COVID-19 pandemic. In our analysis, we follow the ethical framework proposed by Michelle N Meyer and colleagues (2021). We chose this framework as it provides guidance for research institutions on how to coordinate and prioritize research activities in a limited amount of human and material resources (Meyer et al. 2021). It helps to determine clinical trials that are robust enough and feasible to start in the context of specific circumstances triggered by the pandemic.

Amantadine case study

Amantadine has been used in clinical practice since the 1960s. It was originally developed as a prophylactic agent against influenza. Nowadays, amantadine is more commonly known as an antiparkinsonian agent or a therapy for multiple sclerosis–related fatigue (Nisar et al. 2019; UpToDate 2022). Amantadine is approved in many European countries and in the United States. In the face of the COVID-19 pandemic, amantadine joined a long list of medications considered as possible cures for COVID-19. The drug attracted particular attention in Poland.

One of the first reports on the potential efficacy of adamantanes, a group of chemical compounds that includes amantadine and memantine, in the fight against COVID-19 was published in early 2020 (Rejdak and Grieb 2020). The study was a case series analysis of 22 patients who suffered from Parkinson's disease, multiple sclerosis, or cognitive impairment and had confirmed SARS-CoV-2 infections. Those patients took amantadine or memantine as part of the regular treatment of neurological disorders. The authors of the study noted that none of the patients developed clinical manifestations of infectious disease, indicating a potential protective role of adamantanes (Rejdak and Grieb 2020).

In October 2020, one of the European clinics announced on its website that amantadine could treat COVID-19 in 48 h (Optima Outpatient Clinic 2020). The author of the post was a physician from Poland. He shared clinical experience on how the drug Viregyt K (Egis Pharmaceuticals PLC) containing amantadine had helped him and his patients recover from COVID-19. The doctor described a detailed therapeutic scheme he created (Optima Outpatient Clinic 2020). Despite the lack of reliable scientific evidence to prove the hypothesis about amantadine's efficacy, the news was enough to attract not only patient but also healthcare professional attention. In October and November 2020, the number of new cases of COVID-19 significantly increased in Poland (World Health Organization 2022b). Vaccines against COVID-19 were not available at that time. Simultaneously, limited therapeutic options with confirmed activity against COVID-19 were available. Therefore, the information on a new drug that could treat COVID-19 triggered an explosion of public discussion. Soon other anecdotal evidence about the role of amantadine in the treatment of COVID-19 emerged (Wojtasiński 2020; Notes from Poland 2021). No results from clinical trials and only low-quality evidence based on observational (Rejdak and Grieb 2020; Aranda-Abreu et al. 2020, 2021; Mancilla-Galindo et al. 2020; Borra 2020) and preclinical (Smieszek et al. 2020; Abreu et al. 2020) analyses for amantadine use were available. However, the interest in amantadine was tremendous, leading to a substantial increase in the Viregyt K sales in Poland. In October 2020, the sales rose more than three times (from 5000 to 17,000 packages/month) (Ministry of Health 2021).

The widespread off-label use of Viregyt K quickly caused problems with the drug availability on the national level. Patients faced drug shortages. This trend continued even after the health authorities in Poland issued a negative recommendation for amantadine-based COVID-19 treatment (Agency for Health Technology Assessment and Tariff System 2020). The recommendation was based on the results from an observational retrospective study (Mancilla-Galindo et al. 2020) and two case series analyses (Aranda-Abreu et al. 2020; Rejdak and Grieb 2020). Health authorities emphasized that due to the limited scientific evidence and its low reliability, there was a high degree of uncertainty in concluding the efficacy and safety profile of amantadine for COVID-19 treatment. Therefore, in December 2020 the Ministry of Health in Poland imposed a restriction on the sale of Viregyt K. The aim was to ensure access to regular therapy for patients with neurological disorders and to limit the purchase for COVID-19 (Ministry of Health 2020).

In response to the growing interest in the drug and the risk of its widespread use despite the substantial evidentiary gap, the public body, the Medical Research Agency in Poland, funded two non-commercial clinical trials that began in March 2021 (Medical Research Agency in Poland 2021). The goal was to provide evidence and dispel public

Table 1 Characteristics of COV-PREVENT, TITAN and ACT clinical trials that evaluated amantadine as COVID-19 treatment

Acronym of the trial	COV-PREVENT	TITAN	ACT
Trial title	The Use of Amantadine in the Prevention of Progression and Treatment of COVID-19 Symptoms in Patients Infected With the SARS-CoV-2 Virus	Efficacy of Amantadine Treatment in COVID-19 Patients	Amantadine for COVID-19: A Randomized, Placebo Controlled, Double-blinded, Clinical Trial
NCT ID	NCT04854759	NCT04952519	NCT04894617
EudraCT Number	2021-001144-98	2021-000981-13	2021-001177-22
Trial Design	- Phase 3 - Randomized - Double-blind	- Phase 3 - Randomized - Double-blind	- Phase 3 - Randomized - Double-blind
Trial participants	Adult hospitalized and non-hospitalized patients in the early phase of COVID-19 who are at the risk for severe illness	Adult hospitalized patients with moderate or severe COVID-19 in the initial stage of the disease	Non-hospitalized high-risk patients with COVID-19
Intervention	Amantadine	Amantadine	Amantadine
Comparator	Placebo	Placebo	Placebo
Primary outcomes	Clinical deterioration	Time to recovery	Clinical status
Location of trial	Poland	Poland	Denmark
Anticipated number of trial centers	8 centers	20 centers	1 center
Estimated Enrollment	200 participants	500 participants	Unclear – it differs between ClinicalTrials.gov (226 participants) and the European Union Clinical Trials Register (242 participants)
Start Date	Unclear - it differs between ClinicalTrials.gov (March 15, 2021) and the European Union Clinical Trials Register (April 20, 2021)	March 30, 2021	Unclear - it differs between ClinicalTrials.gov (June 1, 2021) and the European Union Clinical Trials Register (April 26, 2021)

concerns about the role of amantadine in COVID-19. One trial (TITAN, NCT04952519) evaluated the efficacy of amantadine in the treatment of hospitalized patients with moderate or severe COVID-19 (ClinicalTrials.gov 2021b). The other (COV-PREVENT, NCT04854759) investigated the efficacy of the drug in the initial phase of COVID-19 with less severe symptoms including patients in an ambulatory setting (ClinicalTrials.gov 2021c). The characteristics of the COV-PREVENT and the TITAN trial design are presented in Table 1. The table reports the information presented in two clinical trial registries: ClinicalTrials.gov and The European Union Clinical Trials Register (EU CTR). It also contains data about the third clinical trial (ACT, NCT04894617) that we found in these registries when searching for studies evaluating amantadine in COVID-19. This study was initiated in Denmark (ClinicalTrials.gov 2021a).

Interest in amantadine continued throughout 2021 and attracted more attention around the world. More preclinical (Fink et al. 2021; Zhou et al. 2021; Toft-Bertelsen et al. 2021a) and observational data (Kamel et al. 2021; Bodnar et al. 2021) emerged. In one study the authors even proposed amantadine as a 'novel, cheap, readily available and effective way to treat COVID-19' (Toft-Bertelsen et al. 2021a). However, this recommendation was based on the results of *in vitro* experiments. As this led to exacerbated misinformation about the drug efficacy, the authors promptly reported a correction to the article (Toft-Bertelsen et al. 2021b).

In February 2022, the preliminary results of the TITAN trial were published in a press release. Data from 149 hospitalized patients (78 received amantadine, 71 received a placebo) were analyzed. No significant differences in efficacy between placebo and amantadine were observed (Notes from Poland 2022). The principal investigator announced the termination of the trial. To our knowledge, as of November 2022, the other two trials (COV-PREVENT and ACT) have not published the trial results yet.

Ethical challenges

The case of amantadine presents an example of an approved drug that attracted attention as a possible treatment or prevention for COVID-19 leading to the launch of clinical trials. According to Meyer and colleagues (2021), the assessment of the legitimacy of the launch of clinical trials should include three consecutive stages. The initial stage should start with the evaluation of four threshold criteria: (i) social value, (ii) scientific validity, (iii) feasibility and (iv) consolidation/collaboration. The second stage should

include the assessment of whether an institution has enough resources to support all trials that fulfill the first stage. If yes – all trials can proceed. If not – the third stage of trials' evaluation is required, which includes additional criteria for prioritization together with study-specific criteria (e.g., promising intervention or institutional expertise) or institution's portfolio diversity criteria. In our analysis of amantadine clinical trials, we focus on the requirements of the first stage (Meyer et al. 2021). Without fulfilling these criteria, no clinical trial should be initiated.

Social value

Social value is one of the fundamental ethical requirements for clinical trials (Wendler and Rid 2017). According to the Council for International Organizations of Medical Sciences (CIOMS) guidelines, it is defined as 'the importance of information that a study is likely to produce' (CIOMS 2016). Clinical research has social value if it contributes to useful knowledge that is expected to promote patient or society health. Although amantadine did not seem more promising than the other COVID-19 drug candidates, there are at least a few reasons why it was important to start clinical trials evaluating this drug. We discuss them in detail in the following sections.

Widespread off-label use of unproven intervention

Amantadine as a treatment for COVID-19 was used outside of the approved indications, which is widely known as off-label use. This is a common strategy in routine clinical practice, particularly in pediatrics (Hoon et al. 2019) and oncology (Saiyed et al. 2017). However, health professionals before prescribing off-label drugs should evaluate the risk-benefit ratio and clinical appropriateness. Their decisions should be supported by solid scientific evidence (Eguale et al. 2016; Maziarz and Stencel 2022). Public health emergencies such as the COVID-19 pandemic, pose a challenge to the medical environment. Effective treatments are urgently needed, whereas gathering evidence takes time. Simultaneously, the initially obtained evidence is regularly confronted with the results of ongoing clinical trials. Although some intervention appears initially promising, the emerging evidence may fail to support it or even indicate a harmful effect. Hence, the use of unproven interventions should be properly regulated and applied with caution. Their usage should comply with an adequate justification, ethical and regulatory oversight, consent process and contribution to evidence (World Health Organization 2022a). In the case of amantadine, the recommendations of the national health authorities did not support its use as COVID-19 treatment due to the limited scientific evidence and its low reliability (Agency for Health Technology Assessment and Tariff System 2020). In view of this, the regular use of unproven intervention should not be justified. Nevertheless, huge public interest in amantadine contributed to a surge in prescriptions. Many doctors prescribed amantadine in response to patient demand (Notes from Poland 2022, 2021). This mechanism was described by the others as "panic prescribing" (Caplan and Upshur 2020). The provision of reliable evidence from clinical trials was very important to support robust clinical decision-making.

Patient safety and uncontrolled use

The high demand for amantadine affected the allocation of the drug. Drug shortage could be a burden for non-COVID-19 patients who needed and benefited from amantadine treatment with confirmed efficacy. To prevent this, Viregyt K sales restrictions were introduced (Ministry of Health 2020). However, this intensified the tensions. Patients tried to obtain the drug on their own (Notes from Poland 2021). Uncontrolled use and self-medication with the drug could pose a real threat to the health and safety of patients. Taking amantadine can result in various side effects. Cardiovascular disorders (e.g. orthostatic hypotension, syncope, peripheral edema) or central nervous disorders (e.g. dizziness, delusions, illusions, hallucinations, paranoia) are very common (UpToDate 2022). On the one hand, it is understandable that patients facing a life-threatening disease are looking for any possible solutions that could help. On the other hand, such action should be prevented. To do so, adequate evidence is required (Caulfield et al. 2021). Results from robust clinical trials would be a strong argument in discussions aimed at minimizing the risk of uncontrolled use of amantadine.

Scientific validity

Scientific validity is an ethical requirement applying to study design and methodology. All research must be well-planned and conducted in a rigorous manner to produce reliable and valid results (Bernabe, van Thiel, and van Delden 216). Pandemic circumstances are challenging for the research environment. Time for gaining evidence and learning is very tight. However, urgent need for an effective therapeutic and speed in collecting the evidence should not justify lowering scientific standards (London and Kimmelman 2020). The following section analyses the scientific validity of research hypotheses and research design associated with amantadine clinical trials.

Research hypothesis

The research hypotheses in clinical trials should be supported by well-grounded evidence and address an important and unresolved question (Zarin, Goodman, and Kimmelman 2019). The choice to test a particular therapeutic target in clinical trials should be well considered and justified, not random. Depending on the phase of drug development, supporting evidence may be related to the pre-clinical or earlier clinical trial results. If the candidate for a new clinical trial is approved, it can also involve results from other post-marketing trials. Firstly, preliminary evidence allows us to assess the risks and benefits ratio for future participants. Secondly, if we decide to verify a particular research hypothesis, we invest human, financial and infrastructural resources. These resources are usually limited. Investing in one of the proposed hypotheses can affect the resources remaining to verify the others (Lynch et al. 2021; Meyer et al. 2021).

Amantadine clinical trials in Poland were initiated mainly in response to social pressure, increased public interest, and media coverage. We assert that the scientific grounds for starting amantadine clinical trials were low quality evidence. Although the scientific value was anticipated to be low, unusually the social value was expected to be high. This was because of significant social interest in the drug. In our view, this strongly supports the need for evidence to justify why amantadine should not be prescribed or privately accessed by interested parties. Otherwise, a lack of evidence-based argument could enhance uncontrolled use of the drug.

Study design

Clinical trials should be designed in a way to provide a meaningful research answer and have sufficient power to detect the positive or negative effects of an evaluated intervention (Zarin, Goodman, and Kimmelman 2019). Considering that, randomized controlled at least double-blinded clinical trials are recommended (Hariton and Locascio 2018; London and Kimmelman 2020; Waligora and Klas 2022). These design requirements were fulfilled by amantadine clinical trials. Moreover, as amantadine has been used in clinical practice for many years, clinical trials started directly from phase 3. This is a very common strategy when testing an already authorized medicine (Verbaanderd et al. 2021). However, flexible research designs could be considered in this case (Park et al. 2021; Vanderbeek et al. 2022). For example, instead of launching new clinical trials, amantadine could be evaluated as one of the arms in already ongoing platform clinical trials. Platform clinical trials enable testing of multiple interventions (or therapeutic schedules) under a single study; they allow arms to be added or dropped during the trial course according to the pre-specified criteria and results of interim analysis (Berry, Connor, & Lewis, 2015). The analysis performed by Vanderbeek et al. (2022) indicates that it is a promising solution for rapid evidence generation. Nevertheless, the inclusion of amantadine in other platform studies would require coordinated collaboration with the other bodies. This could make the process of evaluating the amantadine more complicated, especially since the interest in the drug was mainly national. It is difficult to assess how quickly amantadine could be included as an arm in platform trials that were conducted around the world. In our opinion, choosing the model of randomized, double-blinded clinical trial was appropriate.

Feasibility

Feasibility assessment is a process to determine the possibility of conducting clinical trials from the point of view of the available resources. The aim is to ensure that there is a reasonable probability of achieving the recruitment goals and to answer the research questions. Clinical trials should be launched only if there is sufficient human factor (including patient-participant or research staff availability) and non-human resources (including funding, drug supplies or available infrastructures) to carry out the research (Meyer et al. 2021; Rajadhyaksha 2010).

The COVID-19 pandemic substantially emphasized problems in the conduct and feasibility of clinical trials (Park et al. 2021; Hutchinson, Klas, Carlisle, Kimmelman, et al. 2022; Hutchinson et al. 2022; Lasch et al. 2022; Mitchell et al. 2020). The large number of COVID-19 clinical trials that were launched simultaneously forced competition for resources (the availability of which was already limited due to the heavy burden on the health care system and the large number of COVID-19 patients). As knowledge and understanding of the disease evolved, and as evidence from other studies emerged, some of the research hypotheses were disproven over time. Furthermore, the forecasting of the pandemic dynamics was burdened with a large dose of uncertainty (Ioannidis et al. 2022). Due to the changing nature of the pandemic, the surge and fall in COVID-19 cases, some of the studies were unable to meet their enrollment targets within the specified time frame (Janiaud et al. 2021). Research environments also faced the challenge of ensuring the safety of the clinical trials' operational staff and patients. To increase feasibility, solutions such as remote monitoring of a clinical trial or even remote efficacy and safety assessment of the treatment and home delivery of investigational medicinal products have become popular, if the patients enrolled did not require hospitalization (Leyens, Simkins, and Horst 2022).

When amantadine clinical trials were launched, most of these aspects were already known. The feasibility criterion for the TITAN and COV-PREVENT trials seems to be met. Firstly, for the implementation of research tasks, financial support was provided from the resources of the Medical Research Agency in Poland. Thanks to that, the trial funding was secured. Secondly, both studies in Poland were multicenter. These increase the possibility of achieving the recruitment goals and allocating the necessary resources.

Consolidation and collaboration

Research consolidation and collaboration are broad terms that encompass many aspects of the conduct of clinical trials (Meyer et al. 2021).

First, this requirement deals with cooperation between various institutions involved, including research centers, public-private partnership, and the support provided by regulators. It should be reflected at both regional and international level. The aim is to avoid research waste and maximize the feasibility and efficacy of actions taken (Meyer et al. 2021; Kim and Hasford 2020). In the light of this requirement, the fact that two separate clinical trials evaluating the efficacy of amantadine were launched almost simultaneously in the same country may be questioned. Although the trials tested the efficacy of amantadine in different phases of COVID-19, they could compete for recruitment targets. Furthermore, shortly after the simultaneous start of two clinical trials, another trial in Denmark began to evaluate the efficacy of amantadine in COVID-19. This raises questions about the lack of coordination of research activities at the international level. Given the limited scientific values of the research hypothesis, the number of study participants potentially exposed to this drug should be reduced.

Second, rapid and transparent data sharing contributes to the consolidation of research efforts (Naci et al. 2020; Strzebonska et al. 2020). This applies not only to the sharing of results, but also to research protocols. Especially during a health crisis, it is important to exchange information as quickly as possible. The quality of the reporting varies between amantadine clinical trials conducted in Poland and Denmark. For example, on ClinicalTrials.gov the description of clinical trials conducted in Poland is limited to one or two sentences (ClinicalTrials.gov 2021b, c), while the description of the clinical trial conducted in Denmark is more detailed and comprehensive (ClinicalTrials.gov 2021a). There is also inconsistency between information reported for the trials in the ClinicalTrials.gov and the European Union Clinical Trials Register (EU CTR). The description of TITAN trials seems to be more detailed in EU CTR (e.g. it includes data about secondary endpoints, whereas ClinicalTrials.gov does not), but most data on EU CTR are in the Polish language, which limits its availability (ClinicalTrials.gov 2021b; The EU Clinical Trials Register 2021b). In the case of ACT, the planned number of patients included in the study is different in each registry (at ClinicalTrials.gov there is a number of 226 patients (ClinicalTrials.gov 2021a), whereas at EU CTR – 242 (The EU Clinical Trials Register 2021a)). Importantly, for now, we can learn only from the press materials that in the TITAN study, a drug called remdesivir was used as a standard of care in the experimental and placebo group. It is unclear whether other drugs were also used. Lack of trial transparency disturb the assessment of the credibility and quality of the study for interested parties (e.g., potential participants, other researchers).

Limitations

The following limitations should be considered in our analysis. We built our arguments based on publicly available data. We did not have access to full research protocols and other internal documents shared between the research sponsor and the bioethics committee or the national competent authority. Finally, our article emphasized amantadine trials launched in Poland. We have little information about the study in Denmark. Therefore, we could not accurately describe and compare the situation in both countries.

Conclusion

In this paper, we analyzed the case study of amantadine clinical trials. Despite the lack of high-quality evidence that could prove the drug's efficacy, these clinical trials were launched in response to social demand resulting from the widespread and uncontrolled use of amantadine outside the label. We aimed to discuss whether amantadine clinical trials should have been conducted. To do so, we followed four ethical aspects proposed as threshold criteria for prioritization of COVID-19 clinical trials: social value, scientific validity, feasibility, and consolidation/collaboration (Meyer et al. 2021). Our analysis indicates doubts regarding the fulfillment of individual criteria, especially in terms of scientific validity and quality of evidence supporting the research hypothesis. However, although the scientific value was low, the social value of amantadine clinical trials was extremely high. Launching clinical trials was necessary to gain solid evidence verifying amantadine efficacy. This was important to support the clinical decision-making process while reassuring public concerns. With our article, we join the discussion on the lessons learned from the pandemic. Our findings may help to improve future efforts to decide on the launch

of clinical trials on approved drugs when dealing with the widespread off-label use of the drug.

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Data availability The data used in this article are from publications available in the public domain.

Declarations

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SYSTEMATIC REVIEW

Risk and Benefit for Basket Trials in Oncology: A Systematic Review and Meta-Analysis

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Abstract

Background Oncology research is increasingly adopting new clinical trial models that implement the concept of precision medicine. One of these is the basket clinical trial design. Basket clinical trials allow new treatments to be evaluated across multiple tumor types. Patients recruited to basket clinical trials share certain molecular characteristics of their cancer that are predictive of clinical benefit from the experimental treatment.

Objective Our aim was to describe the risks and benefits of basket clinical trials in oncology.

Methods Our study was prospectively registered in PROSPERO (CRD42023406401). We systematically searched PubMed, Embase, and ClinicalTrials.gov for reports of basket clinical trials in oncology published between 1 January, 2001, and 14 June, 2023. We measured the risk by treatment-related adverse events (grades 3, 4, and 5), and the benefit by objective response rate. We also extracted and analyzed data on progression-free survival and overall survival. When possible, data were meta-analyzed.

Results We included 126 arms of 75 basket clinical trials accounting for 7659 patients. The pooled objective response rate was 18.0% (95% confidence interval [CI] 14.8–21.1). The rate of treatment-related death was 0.7% (95% CI 0.4–1.0), while 30.4% (95% CI 24.2–36.7) of patients experienced grade 3/4 drug-related toxicity. The median progression-free survival was 3.1 months (95% CI 2.6–3.9), and the median overall survival was 8.9 months (95% CI 6.7–10.2).

Conclusions Our results provide an empirical basis for communicating about the risks and benefits of basket clinical trials and for refining new models of clinical trials applied in precision medicine.

Key Points

To our knowledge, this is the first systematic review with meta-analysis that provides data on both benefits and risks of basket clinical trials in oncology.

We found that the pooled objective response rate for all 126 included studies was 18.0%. The median progression-free survival was 3.1 months, and the median overall survival was 8.9 months. The overall drug-related death rate was 0.7% and 30.4% of patients experienced grade 3–4 drug-related adverse events.

The studies were heterogeneous in terms of the availability of results for the various outcomes of interest in our systematic review. Objective response rates were relatively well reported, but not progression-free survival, overall survival, or drug-related adverse events.

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1 Introduction

Advances in cancer genetics and progress in drug development toward molecularly targeted agents have stimulated changes in the design of clinical trials in oncology [1–5]. In the traditional approach, cancer clinical trials typically evaluate an experimental treatment in a group of patients with the same cancer location or histology [1, 6]. However, the evaluation of new experimental treatments is now moving away from the organ-oriented model. An emerging practice in medicine known as precision medicine is becoming increasingly important. Rather than categorizing patients based solely on the anatomic origin of their cancer, personalized medicine involves tailoring treatments to the genetic and molecular characteristics of the tumor [1, 6]. The rationale is that a therapy tailored to the molecular alteration within the tumor should provide greater therapeutic benefit to the patient.

New clinical trial models that implement the concept of precision medicine are becoming more common in oncology research [3, 6–8]. Examples include umbrella and basket clinical trials (BCTs). An umbrella trial is a type of clinical trial design that aims to test a drug or drugs within the same cancer type but with different molecular biology. Patients enrolled in an umbrella trial receive treatment based on the specific mutation or biomarker of their cancer [9–11]. In contrast to umbrella trials, basket trials allow the evaluation of new treatments across multiple tumor types (including rare tumors), regardless of their location, and the criterion for patient inclusion is based on the presence of a specific biomarker or molecular alteration. Patients with different types of cancer recruited to BCTs share certain molecular characteristics that are potentially predictive of clinical benefit from the experimental treatment [1, 10, 12].

Both basket and umbrella studies give opportunities to evaluate new therapies more quickly and effectively as new drugs may be added while the trial is still ongoing [13, 14]. The number of these clinical trials is increasing. In addition, they have contributed to the approval of new cancer drugs [8, 15]. As the number of patients enrolled in precision oncology trials continues to grow, it becomes increasingly important from a bioethical perspective to assess the risk-benefit profile to inform future trial participants and stakeholders [1, 3, 10]. Although some studies have reported that biomarker-selected patient populations have better response rates than non-biomarker-selected patient populations, this does not reflect the impact of a specific clinical trial design [16, 17]. Previously, we published a systematic review and meta-analysis of the risks and benefits of umbrella trials [11]. In the following, we focus on BCTs. Basket trial design is usually more flexible and may allow for adaptation to the accumulating data compared with the traditional clinical trial design [18]. Basket clinical trials are expected to have higher response rates than standard designs [14, 15]. The main reason for this is that patients recruited to BCTs share certain molecular characteristics and the trial is "tailored" to them. If an arm of a therapy being tested is discontinued (e.g., because of unacceptable toxicity and a lack of evidence of benefit), patients may be transferred to other ongoing arms of the trial (if the clinical trial protocol allows). Interim analyses of the collected data may allow optimization of the allocation of patients to the most promising and relevant arm, which may enhance patients' benefit. Basket clinical trials mostly test a targeted therapy, and the treatment is tailored to the specific markers believed to be predictive of success [8, 14, 18]. Overall, the basket trial design components (e.g., genetic screening to confirm the presence of a specific biomarker, tailoring the treatment to the molecular changes, interim analyses) may have an impact on the benefit of tested therapies on patients. It is not necessarily justified to anticipate a reduction in the adverse event (AE) rate in basket trials in comparison to a standard design. However, should BCTs yield a higher response rate, the overall risk-to-benefit ratio will be more favorable, even if the AE rate is comparable to that of a standard design. We conducted our systematic review with meta-analysis to measure the benefit and toxicity rates in BCTs in oncology as this issue has not been explored yet.

2 Methods

Our protocol was prospectively registered in PROSPERO (CRD42023406401). We adapted and expanded methods from our previous analyses of risk and benefit in oncology clinical trials [11, 19, 20]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting guidelines (see the PRISMA checklist in the Electronic Supplementary Material [ESM]) [21].

2.1 Eligibility Criteria

We included original reports (abstracts, articles, and summary reports on ClinicalTrials.gov) with results of interventional clinical trials with a basket design in oncology. Specifically, we looked for trials recruiting adult patients with different types of cancer (at least two cancer types) that tested an intervention based on the molecular profiling of cancer, rather than the location or histology of the cancer. We included both matched studies in which a mutation in a specific biomarker was confirmed and non-matched studies, i.e., studies that confirmed a lack of presence of a mutation in a specific biomarker. Both single-arm and multi-arm trials of all phases that met our criteria were included. We also considered parts of complex trials, for example, platform

studies or multi-stage trials, where only a selected study part met the criteria for a basket trial.

Both solid tumors and hematological malignancies were eligible. In terms of interventions, we included targeted therapy, immunotherapy, or combinations of these, evaluated for cancer treatment. We had intended to include studies testing chemotherapy, but none of these studies met the other eligibility criteria. We considered only studies that reported results on treatment-related toxicity (e.g., number of patients with grade 3 and/or 4 and/or 5 treatment-related AEs) and/or treatment response (e.g., objective response rate, number of patients with partial responses).

We excluded studies that recruited pediatric populations, healthy volunteers, or patients with only one cancer type. We also excluded trials without a basket design and studies that did not perform molecular profiling to find a specific molecular alteration in tumors. The full eligibility criteria relevant to the Population, Intervention, Comparator, Outcomes and Study Type (PICOS) framework are listed in Table 1 of the ESM.

2.2 Data Sources and Search Strategy

We systematically searched Embase, PubMed, and ClinicalTrials.gov for interventional cancer BCTs published between 1 January, 2001 and 14 June, 2023 (see our search strategies in Table 2 of the ESM). We did not apply language restrictions. We checked our strategies using the Canadian Agency for Drugs and Technologies in Health peer-review checklist for search strategies [22].

We performed additional searches of conference proceedings found in the records retrieved from Embase and PubMed. We also searched for other eligible trials in the reference lists of included articles and relevant review papers. For all studies included in the full-text screening, we searched for the ClinicalTrials.gov ID (NCT number) to check the trial description and results on ClinicalTrials.gov.

2.3 Study Selection Process

We selected trials in a stepwise process. Three review authors (KK, KS, LZ) screened the records for the initial study inclusion. Then, six reviewers (KK, KS, LZ, AW, TK, UBK) performed the screening of full texts and checked other resources (conference proceedings, reference lists, and records on ClinicalTrials.gov). At each step, the records were merged, and duplicates removed. Each study report was assessed for inclusion by two researchers independently. Disagreements were resolved by discussion and, if necessary, a third person, an arbiter (MW), was involved.

2.4 Data Extraction

The specific unit for data extraction was an "arm" of a BCT. The arm referred to each subgroup of patients with different cancer types who received a specific intervention (or combination therapy) that was matched or not matched (non-match arm) to the specific biomarker (or group of biomarkers). A basket trial could have more than one arm (e.g., more than one intervention matched to a biomarker, or a specific intervention matched to more than one specific biomarker, or both). For the purposes of this article, the term "arm" is used interchangeably with "study" when reporting results.

The information provided on ClinicalTrials.gov supported data extraction. Each arm of the basket trial could have a separate registration and individual NCT number in the ClinicalTrials.gov registry, or there was one registration number for all arms of a basket trial. We extracted data from each arm separately (regardless of the registration type).

For each basket study arm, we merged information from all available sources (abstract, article and/or record(s) on ClinicalTrials.gov). As each source could report different results, we extracted data from (whichever came first): (a) the latest or the final report or (b) we chose the source with results reported for the highest number of patients or (c) with the most detailed information about the outcomes of interest.

We created and piloted our data extraction form. Its final version is available from the Open Science Framework, https://osf.io/w4ke9/. For each study arm, we extracted data related to study characteristics (e.g., phase, funding, location, study status), patient characteristics (e.g., number of enrolled participants, age, cancer type and stage of disease), intervention (e.g., agent names, type of therapy), and outcomes (e.g., objective responses, drug-related grade 3–5 AEs). Data were extracted independently by experienced reviewers working in pairs (KK, KS, LZ, AW, TK, or UBK). We resolved the discrepancies by discussion and, if necessary, an arbiter (MW) was involved. An experienced oncologist had a supervisory role (SVW).

2.5 Data Curation

We measured surrogate benefit using the objective response rate (ORR). We defined the ORR as the proportion of participants with a partial or complete response as defined by the study authors. We calculated the ORR as the sum of both partial and complete responses, or the ORR was reported directly in the study. For other benefit measures, we collected median progression-free survival (PFS) and overall survival (OS) data.

To assess risk, we used data on grade 3, 4, or 5 drug-related AEs as defined by the Common Terminology Criteria for Adverse Events version 5.0 (or earlier versions) [23]. We

assessed separately the number of treatment-related AEs and the proportion of patients who experienced them. We considered an AE as related to the study drug if it was clearly stated by the study authors. Expressions such as "AEs at least possibly related to study therapy" or "AEs suspected to be drug-related" or "AEs attributed to treatment" or "AEs possibly or probably related to study drug" were also acceptable. If an AE was not clearly described as treatment related, we excluded it from the risk analysis.

2.6 Risk of Bias (RoB) Assessment

We assessed the risk of bias (RoB) for each basket study arm with the results published in the article/s. We did not perform RoB assessments for other data sources (abstracts or summary of results in the ClinicalTrials.gov registry) as they usually provide limited information to conduct comprehensive RoB. We adapted the Cochrane RoB tools for non-randomized trials as all included studies were non-randomized [24]. Two researchers (KK, KS, LZ, AW, TK, or UBK) independently performed RoB directly after data extraction. Whenever any discrepancies occurred, we discussed and resolved them.

2.7 Statistical Analysis

We calculated rates of objective response, rates of grade 5 (death), and grade 3–4 drug-related AEs by dividing the number of patients who experienced the outcome(s) by the total number of patients evaluated for response or toxicity in this arm. We estimated pooled rates by a meta-analysis for proportion. We performed a meta-analysis when results for a particular outcome were available from at least two studies. We used random-effects modeling and the restricted maximum likelihood estimator to account for heterogeneity between studies. We calculated the I^2 statistic to provide a measure of the proportion of overall variation that is due to heterogeneity between studies. Differences in response rates and grades 5 and 3–4 drug-related AEs rates between the categories of phase, type of therapy, number of drugs evaluated, cancer types, and funding were assessed using the Q test for heterogeneity in meta-regression. We present results as rates with a 95% confidence interval (CI) in each category and a P value from the Q test for heterogeneity in meta-regression. Unweighted median with 95% CI was calculated for PFS and OS by bootstrap methods using the "boot" package in the R software [25] and compared between categories using the Mann–Whitney test or Kruskal–Wallis test. We performed a meta-analysis using the metafor package (R Version 4.3.2). $P < 0.05$ was considered statistically significant. All tests were two-sided.

3 Results

We retrieved a total of 4722 records from PubMed and Embase and 310 records from the ClinicalTrials.gov registry for review. After additional screening of conference abstracts and citations, we finally included 180 unique reports that met our eligibility criteria (see PRISMA flow diagram, Fig. 1). This resulted in 126 unique BCT arms for our systematic review and data extraction, which were part of 75 unique BCTs. We present a characteristic of included studies with references in the Table 3 of the ESM.

3.1 Characteristics of the Basket Trials' Arms

We summarized the characteristics of included basket trial arms in Tables 1 and 3 of the ESM. The vast majority (124, 98.4%) were matched arms and two (1.6%) were non-matched. Most were phase II studies (86, 68.3%). The others were registered as phase I (28, 22.2%) or phase I/II studies (12, 9.5%). All arms were non-randomized. More than half were industry funded (67, 53.2%) and conducted in North America (68, 54.0%). Targeted therapy was evaluated in 106 (84.1%) arms, immunotherapy in 14 (11.1%) arms, and a combination of both in six (4.8%) arms. Basket trial arms mainly evaluated one drug (104, 82.5%), others evaluated two drugs (22, 17.5%). A total of 85 different interventions or unique drug combinations were tested in 126 basket trial arms. These were matched to a total of 67 unique biomarkers (or their combination). Further studies were recommended in 84 (66.7%) arms.

3.2 Patients' Characteristics

We provide baseline characteristics of the 7659 enrolled patients in Table 1. The median enrollment per study was 35 (interquartile range: 18–62). The median age of participants was at least 60 years in 44 (34.9%) studies, and less than 60 years in 18 (14.3%) studies, and in the remaining 64 (50.8%) studies, the median age was not reported. Patients with solid tumors were recruited in 110 (87.3%) arms, hematological in two (1.6%) arms, and both in 14 (11.1%) arms. Most studies used the Eastern Cooperative Oncology Group/World Health Organization/Zubrod Scale to assess patient performance status, and 77 (61.1%) recruited patients with an Eastern Cooperative Oncology Group/World Health Organization/Zubrod Scale 0–1 status.

3.3 Pooled Analysis of Benefit

A total of 105 studies reported ORRs. There were 1230 objective responses reported in 6020 patients evaluated.

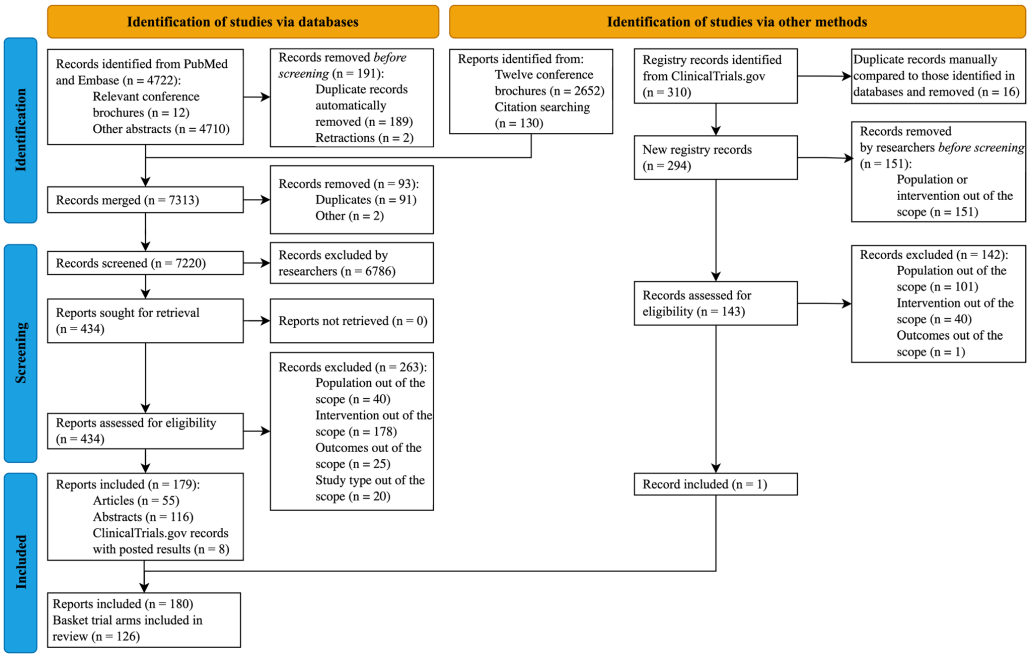

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The number of identified, screened, and included records

The pooled ORR was 18.0% (95% CI 14.8–21.1) (Table 2). Objective response rate results were very heterogeneous and varied widely between studies ($I^2 = 95.2$, see Table 4 of the ESM). Partial and complete responses were reported separately for 103 and 88 studies, respectively. We found that 1.4% (95% CI 1.0–1.8, $I^2 = 8.0$) of participants evaluated in BCTs experienced a complete response and 13.7% (95% CI 11.5–15.9, $I^2 = 87.2$) experienced a partial response.

We performed subgroup analyses based on study phase, funding type, therapy type, number of investigational agents, and cancer type (Tables 2 and 4 of the ESM). We found significant differences in ORRs based on the study phase ($P = 0.005$) and cancer type ($P = 0.004$). Hematologic malignancies had a higher ORR than solid tumors or a combination of both. There was a higher ORR in phase I/II trials and in phase I rather than phase II trials. One of the two hematological studies was phase I and the other was phase I/II. Therefore, we performed the analysis separately for the solid tumor studies (see Table 5 of the ESM) to evaluate whether the relatively high responses observed in the hematological studies impacted the outcome of the phase differences. Nevertheless, the phase results obtained for solid tumors only were analogous. There were no significant differences in ORRs between other subgroups.

The median PFS was reported in 51 of 126 arms analyzed, while the median OS was reported in 40 of 126 arms. The pooled median PFS was 3.1 months (95% CI 2.6–3.9). The pooled median OS was 8.9 months (95% CI 6.7–10.2). The results of the subgroup analysis are presented in Table 3. For median PFS, we found statistically significant differences within the study phase ($P = 0.013$) and cancer type ($P = 0.004$). Median PFS was shorter in phase II than in phase I and in studies recruiting both hematological and solid tumors than in studies recruiting solid tumors only. Median PFS was not reported for hematological malignancies. We did not observe statistically significant differences in median OS between subgroups.

3.4 Pooled Analysis of Risk

A total of 56 studies reported data on grade 5 drug-related AEs. No drug-related deaths were observed in 45 studies, while 11 studies reported one to three deaths. Out of 3247 patients evaluated, 18 drug-related deaths were reported. The pooled rate of drug-related death was 0.7% (95% CI

Table 1 Characteristics of included basket trials' arms

Characteristics	Category or number	Total ($n = 126$), n (%)
Study phase	Phase II	86 (68.3)
	Phase I	28 (22.2)
	Phase I/II	12 (9.5)
Arm type	Experimental, matched	124 (98.4)
	Experimental, non-matched	2 (1.6)
Arm status	Ongoing	67 (53.2)
	Completed	43 (34.1)
	Terminated	14 (11.1)
	Not reported	2 (1.6)
Funding	Industry	67 (53.2)
	Non-industry	35 (27.8)
	Partial industry	22 (17.5)
	Not reported	2 (1.6)
Location	North America	68 (54.0)
	Mixed	39 (31.0)
	Asia	7 (5.6)
	Europe	6 (4.8)
	Not reported	6 (4.8)
Type of therapy	Targeted therapy	106 (84.1)
	Immunotherapy	14 (11.1)
	Targeted therapy and immunotherapy	6 (4.8)
Number of drugs	1 drug	104 (82.5)
	2 drugs	22 (17.5)
Cancer type	Solid	110 (87.3)
	Solid and hematological	14 (11.1)
	Hematological	2 (1.6)
Stage of disease[a]	Advanced or metastatic or relapsed	93 (73.8)
	Early or locally advanced or advanced or metastatic or relapsed	33 (26.2)
Performance status scale used	ECOG/WHO/Zubrod 0–1	77 (61.1)
	ECOG/WHO/Zubrod 0–2	36 (28.6)
	ECOG/WHO/Zubrod 0–4	5 (4.0)
	Karnofsky Performance Status	1 (0.8)
	Not reported	7 (5.6)
Median age of enrolled patients, years	≥ 60	44 (34.9)
	< 60	18 (14.3)
	Not reported	64 (50.8)
Median lines of prior therapy	> 2	38 (30.2)
	1–2	11 (8.7)
	Not reported	77 (61.1)
Further studies recommended	Yes	84 (66.7)
	No	7 (5.6)
	Not reported	35 (27.8)
Enrolled patients, n (%)[b]	7659 (100)	
Evaluated patients, n (%)	7389 (96.5)	
Patients evaluable for response	6020 (78.6)	
Patients evaluable for toxicity	3247 (42.4)	
Female patients, n (%)[c]	2891 (37.7)	
Median number of enrolled patients per study (IQR)	35 (18–62)	

ECOG Eastern Cooperative Oncology Group, *IQR* interquartile range, *WHO* World Health Organization

[a]The present study did not include any studies that evaluated only early or locally advanced cancer

[b]For six studies, the number of patients enrolled was not reported; therefore, the number of patients evaluated was used in the calculation

[c]Gender not reported in 50 arms

Table 2 Number of arms and pooled estimates of rates of response (objective, complete, partial) overall and by subgroups

Subgroup	Objective response		Complete response		Partial response	
	No.	Rate, % (95% CI)	No.	Rate, % (95% CI)	No.	Rate, % (95% CI)
Overall	105	18.0 (14.8–21.1)	88	1.4 (1.0–1.8)	103	13.7 (11.5–15.9)
Phase						
I	20	26.9 (20.0–33.7)	16	0.7 (0.2–1.2)	22	17.8 (13.1–22.5)
I/II	5	27.1 (11.8–42.5)	3	3.2 (0.0–8.2)	9	15.8 (7.4–23.9)
II	80	15.1 (11.6–18.6)	69	1.6 (1.2–2.1)	72	12.2 (9.6–14.8)
P value[a]	0.005		0.023		0.108	
Funding						
Industry	51	21.2 (16.8–25.6)	36	1.1 (0.7–1.5)	49	15.4 (12.3–18.5)
Non-industry	31	13.6 (7.7–19.6)	30	1.8 (0.8–2.7)	32	11.1 (7.0–15.1)
Partial industry	22	16.6 (9.9–23.4)	21	1.9 (1.1–2.8)	21	13.8 (9.0–18.5)
P value[a]	0.118		0.157		0.248	
Type of therapy						
Targeted therapy	90	17.9 (14.4–21.3)	77	1.3 (0.9–1.7)	88	13.5 (11.1–15.8)
Immunotherapy	12	19.1 (9.7–28.5)	10	1.9 (0.8–3.0)	11	15.4 (8.7–22.2)
Targeted therapy and immunotherapy	3	16.9 (0.0–36.0)	N/A		4	13.1 (0.8–25.3)
P value[a]	0.964		0.285		0.864	
Number of drugs						
One	90	16.8 (13.5–20.1)	78	1.3 (0.9–1.7)	87	13.0 (10.6–15.3)
Two	15	24.8 (16.5–33.2)	10	1.9 (0.8–3.0)	16	17.6 (11.9–23.4)
P value[a]	0.079		0.337		0.138	
Cancer type						
Hematological	2	63.6 (36.3–90.9)	2	56.7 (39.4–74.0)	2	12.6 (0.0–32.2)
Mixed	13	15.8 (7.5–24.0)	9	1.7 (0.5–2.8)	10	11.9 (5.1–18.7)
Solid	90	17.5 (14.3–20.8)	77	1.3 (1.0–1.7)	91	13.9 (11.6–16.3)
P value[a]	0.004		< 0.001		0.858	

CI confidence interval, *N/A* not applicable (results reported for one study only)

[a] *P* value for the test of heterogeneity in the rates between subgroups

0.4–1.0, I^2 = 2.1) [Tables 4 and 6 of the ESM]. Grades 3-4 drug-related AEs were reported in 33 studies in 2089 patients. We found that overall, 30.4% (95% CI 24.2–36.7, I^2 = 92.1) of patients experienced grade 3/4 drug-related AEs. For those studies (n = 33) that independently reported combined drug-related grade 3/4 and grade 5 data, we found that the rate of toxicity was 28.6% (95% CI 22.4–34.9, I^2 = 92.3).

As with the ORR, we performed subgroup analyses using the same variables (Table 4). We observed no significant difference in the rates of drug-related deaths between subgroups. However, we found that there was a significant difference in drug-related grade 3/4 and grade 3–5 with respect to the type of therapy. A higher rate of toxicity was observed in patients treated with targeted therapy rather than immunotherapy. No significant differences were observed for other variables.

3.5 Direct Comparison of Risk and Benefit

For the direct risk-benefit assessment, we identified 49 of 126 studies that reported both ORR and drug-related death (grade 5 AEs) [see Table 7 of the ESM]. We found that the pooled ORR was 17.4% (95% CI 13.0–21.9, I^2= 94.6) and the drug-related death rate was 0.8% (95% CI 0.5–1.2, I^2 = 0). In a subgroup analysis, we found that the ORR was higher in studies evaluating two drugs than in arms evaluating one drug. Other subgroup analyses did not show statistically significant differences.

3.6 RoB Assessment

We performed the RoB analysis for the 44 studies for which the main source of data extraction was at least one

Table 3 Number of arms and pooled estimates of median overall survival and progression-free survival overall and by subgroups

Subgroup	Overall survival		Progression-free survival	
	No.	Median (95% CI) [months]	No.	Median (95% CI) [months]
Overall	40	8.9 (6.7–10.2)	51	3.1 (2.6–3.9)
Phase				
I	N/A		5	5.4 (3.6–7.2)
I/II	N/A		N/A	
II	38	8.6 (0.7–10.0)	45	3.0 (2.5–4.0)
P value[a]			0.013	
Funding				
Industry	9	13.3 (7.6–20.3)	18	3.1 (0.8–4.2)
Non-industry	19	7.3 (4.1–8.1)	20	3.4 (3.0–4.8)
Partial industry	12	9.6 (7.0–11.0)	13	2.3 (1.5–2.6)
P value[a]	0.202		0.796	
Type of therapy				
Targeted therapy	36	8.6 (6.8–10.0)	43	2.6 (1.6–3.3)
Immunotherapy	3	9.9 (2.4–11.6)	4	4.8 (2.7–6.5)
Targeted therapy and immunotherapy	N/A		4	3.6 (3.1–5.4)
P value[a]	0.510		0.252	
Number of drugs				
1 drug	35	8.5 (6.5–9.7)	43	2.6 (1.6–3.2)
2 drugs	5	11.7 (5.2–15.3)	8	3.6 (1.9–4.1)
P value[a]	0.145		0.181	
Cancer type				
Mixed	6	7.4 (6.2–8.9)	10	1.8 (1.4–2.0)
Solid	34	9.2 (7.3–10.4)	41	3.5 (3.2–4.0)
P value[a]	0.544		0.004	

CI confidence interval, *N/A* not applicable (results reported for one study only)

[a] *P* value for the Mann–Whitney test or Kruskal–Wallis test

article. Because all included studies were non-randomized, we used the Cochrane RoB tool for non-randomized trials [24]. Overall, RoB was moderate or serious in all studies analyzed. Serious levels of RoB were mainly due to bias because of confounding. See Fig. 1 of the ESM for more details.

4 Discussion

To our knowledge, this is the first systematic review with meta-analysis that provides data on both the benefits and risks of BCTs in oncology. Previously published studies have reported response rates indicating overall response rates of 23% [15] and 14% [26] and 25% [27] for BCTs, without reference to rates related to AEs experienced by patients during treatment. In this study, we extracted data on different benefit measures: partial and complete responses, ORR, PFS, and OS. We found that the pooled ORR for all 126 included studies was 18.0% (95% CI 14.8–21.1). The median PFS was 3.1 months (95% CI 2.6–3.9), and the median OS was 8.9 months (95% CI 6.7–10.2). To measure risk, we extracted data on grade 3, 4, or 5 drug-related AEs. The overall drug-related death rate (grade 5 AEs) was 0.7% (95% CI 0.4–1.0) and 30.4% (95% CI 24.2–36.7) of patients experienced grade 3–4 drug-related AEs. The rate of grade ≥ 3 AEs was 28.6% (95% CI 22.4–34.9).

We performed an additional assessment for matched studies only (excluding two non-matched studies). The ORR for matched studies only was 18.3% (95% CI 15.2–21.5), with grade 5 AEs of 0.7% (95% CI 0.4–1.0) and grade ≥ 3 AEs of 29.3% (95% CI 23.0–35.6) [see Tables 8 and 9 of the ESM]. The results obtained align closely with those reported for all studies in our cohort. The analysis was performed for ORR and treatment-related AEs. In the case of PFS and OS, the

Table 4 Number of arms and pooled estimates of rates of treatment-related adverse events, overall and by subgroups

Subgroup	Grades 3–4		Grades 3-5		Grade 5	
	No.	Rate, % (95% CI)	No.	Rate, % (95% CI)	No.	Rate, % (95% CI)
Overall	33	30.4 (24.2–36.7)	33	28.6 (22.4–34.9)	56	0.7 (0.4–1.0)
Phase						
I	11	25.7 (15.3–36.1)	14	27.0 (17.4–36.6)	13	0.8 (0.3–1.3)
I/II	2	22.4 (0.0–47.2)	2	22.5 (0.0–47.9)	4	0.3 (0.0–0.8)
II	20	34.2 (26.0–42.4)	17	30.9 (21.9–40.0)	39	0.9 (0.5–1.4)
P value[a]	0.367		0.745		0.198	
Funding						
Industry	16	25.4 (17.3–33.6)	20	26.5 (18.6–34.4)	26	0.6 (0.3–0.9)
Non-industry	8	29.5 (16.2–42.8)	8	30.9 (17.0–44.9)	23	1.7 (0.8–2.7)
Partial industry	8	40.9 (28.4–53.4)	4	32.1 (14.3–50.0)	6	1.5 (0.0–3.2)
P value[a]	0.127		0.777		0.054	
Type of therapy						
Targeted therapy	30	32.9 (26.8–38.9)	29	31.7 (25.6–37.8)	51	0.7 (0.4–1.0)
Immunotherapy	3	7.6 (0.0–25.3)	4	7.9 (0.0–23.1)	4	1.2 (0.0–2.9)
P value[a]	0.008		0.004		0.596	
Number of drugs						
1 drug	29	30.7 (24.0–37.3)	29	28.6 (22.0–35.3)	48	0.7 (0.4–1.0)
2 drugs	4	28.5 (9.0–48.0)	4	28.6 (9.0–48.2)	8	1.4 (0.0–2.8)
P value[a]	0.839		0.994		0.337	
Cancer type						
Mixed	2	40.8 (16.1–65.6)	2	43.5 (18.7–68.3)	5	0.8 (0.0–2.0)
Solid	31	29.7 (23.3–36.2)	30	28.0 (21.5–34.5)	51	0.7 (0.4–1.6)
P value[a]	0.393		0.236		0.909	

CI confidence interval

[a] *P* value for the test of heterogeneity in the rates between subgroups

data presented in the article refer to matched studies only, as data for these outcomes were not reported in the case of non-matched studies.

There was a lack of consistency in the reporting of individual endpoints, with some data being readily accessible while others were severely limited. Objective response rates were reported in 105 studies (83.3%), but data for median PFS and OS were reported in only 51 (40.5%) and 40 (31.7%) studies, respectively. While it is a common practice in cancer clinical trials, particularly at the early stages, to extrapolate patient benefit in terms of response rates, we acknowledge that these data should be treated with caution and they are a subject of ongoing discussion [28, 29]. Risk endpoints were also poorly reported. Only 56 studies (44.4%) reported grade 5 treatment-related AEs, and 33 studies (26.2%) reported grades ≥ 3 AEs. In many cases, it was not clear whether the reported AEs were directly related to treatment, making it difficult to use the data. In addition, the results for ORR and grade ≥ 3 AEs were characterized by high heterogeneity ($I^2 = 95.2$ and $I^2 = 92.3$, respectively). Only drug-related death (grade 5 AEs) had low heterogeneity in the available results ($I^2 = 2.1$). High heterogeneity was reduced only in some subgroup analyses.

Although we did not restrict the inclusion and exclusion criteria to early-phase trials, all of the included studies were, at the most, phase II trials. This may support the hypothesis that basket studies are particularly common in the early phases of clinical trials [12]. The much higher response rate in hematologic malignancies is consistent with other risk-benefit analyses of oncology trials [19, 20]. This correlates with the different biology of these types of malignancies and different methods of response assessment.

In addition, our results obtained for phase I differ from those reported by other authors. We found that the ORR for phase I studies was 26.9% (95% CI 20.0–33.7). In another systematic review with meta-analysis of phase I trials of targeted single-agent anti-cancer therapies, the ORR for trials with biomarker eligibility criterion was 12.0% (95% CI 7.3–17.6) and for trials without biomarker eligibility criterion was 4.0% (95% CI 2.5–5.7) [16]. The other report reflects a median overall response rate of 9.4% (interquartile

range: 6–14%) for phase I trials in oncology [30]. This comparison supports the use of biomarker-driven basket trial design in terms of ORR results that patients can achieve in phase I. The median PFS rates also support a greater benefit for phase I participants than for phase II participants. Unfortunately, because of the paucity of OS data, we were unable to assess whether such a relationship exists between phase I and phase II for survival outcomes.

We did not find higher response rates in phase II basket studies compared to other phase II trials without a basket design. The ORR for phase II basket studies in our meta-research was 15.1% (95% CI 11.6–18.6). This result is similar to a pooled ORR of 14.0% (95% CI 6.9–21.2) in phase II umbrella studies [11] and also similar to the median overall response rate of 12.7% (95% CI 11.6–13.9) in standard phase II single-agent studies [31]. However, a higher median response rate was observed for classical phase II trials that tested personalized therapies than for trials without a personalized approach, 31.0% versus 10.5% [31]. The pooled ORR in phase II trials of immune checkpoint inhibitors was 23% [32] and the ORR for pediatric trials testing targeted therapies was 24.4% (95% CI 14.5–34.2) [19].

We observed a higher rate of grade 3–5 toxicity in patients treated with targeted therapy versus immunotherapy, with rates of 31.7% (95% CI 25.6–37.8) versus 7.9% (95% CI 0.0–23.1), respectively. These results should be viewed with caution. First, drugs that target a specific molecular alteration usually have a multi-directional mechanism of action. In many cases, it is difficult to clearly separate immunotherapies from targeted therapies. Second, the results were available only for 26.2% of analyzed studies. Nevertheless, these results and the overall grade 3–5 toxicity rate of 28.6% (95% CI 22.4–34.9) differ from other reports. For example, in a study evaluating treatment-related AEs of PD-1 and PD-L1 inhibitor-based combination therapies, the rate was 47.3% (95% CI 37.3–57.5) in the targeted therapy combination and 35.9% (95% CI 29.5–42.9) in the immunotherapy combination [33]. In another report, evaluating treatment-related AEs of immune checkpoint inhibitors (including CTLA-4, PD-1, and PD-L1 inhibitors) in cancer clinical trials, the incidence of grade ≥ 3 AEs was 38.2% (95% CI 33.6–42.8) [34]. In the study evaluating antibody-drug conjugates, the overall incidence of grade ≥ 3 treatment-related AEs was 46.1% (95% CI 45.2–47.0) [35]. The overall rate of fatal AEs (grade 5) related to treatment in our systematic review was 0.7% (95% CI 0.4–1.0). This is consistent with other analyses of fatal toxicities associated with immune checkpoint inhibitors, which have ranged from 0.3 to 1.3% of treated patients [36].

In a direct comparison of risk and benefit, we found a higher response rate in dual-agent trials than in single-agent trials. This is consistent with the results of our previous systematic reviews, which showed a better response with combination therapy than with single therapy [19, 20]. Our results of the overall risk-benefit analysis for the BCTs are similar to those we obtained for umbrella trials [11]. In the umbrella trials, the overall response rate was 17.7% (95% CI 9.2–25.9) and the overall drug-related death rate was 0.8% (95% CI 0.3–1.4). Basket studies generally performed better in terms of grade 5 drug-related AEs. Deaths occurred in 1 in 125 participants in the umbrella studies and in 1 in 135 participants in the basket studies. We found a similar pattern in terms of median PFS and OS. The median PFS for the umbrella studies was 2.4 months (95% CI 1.9–2.9), compared with 3.1 months (95% CI 2.6–3.9) for the BCTs. Median OS for the umbrella studies was 7.1 months (95% CI 6.1–8.4) and for the basket studies was 8.9 months (95% CI 6.7–10.2). However, our pooled ORR (18.0%) for basket studies differs from the results of other systematic reviews including single biomarker trials. For example, in an analysis of $KRAS^{G12C}$ inhibitors in patients harboring $KRAS^{G12C}$ mutation, pooled ORR was 28.6% (95% CI 21.2–36.6) [37] and for US Food and Drug Administration-approved $KRAS^{G12C}$ inhibitors it was 31% (95% CI 25–37) [38]. The results of the meta-analysis for trastuzumab deruxtecan among HER2-expressing solid tumors indicate an ORR of 47.91% (95% CI 35.16–60.65) [39].

The obtained results indicate that despite the use of precision medicine strategies, where treatment is selected based on the biomarker that drives the disease, nearly four out of five patients in both the basket and umbrella trials still did not respond partially or completely to treatment. Precision oncology trials can lead to hope that the goal of the trial is to provide personalized care based on the patient's best interest and direct therapeutic benefit. As such, it increases the risk of therapeutic misconception [10]. Therefore, proper communication of the potential outcomes of treatment response to the patient is very important to enhance understanding of the study goals and support informed participation. Basket clinical trials are subject to additional constraints. They recruit patients with different types of cancers that have the same type of biomarker mutation. Because of the molecular complexity of cancer, it is unlikely that a single targeted agent or combination will be suitable for every patient with cancer. The same type of mutation may not have the same effect on all tumor types, which may affect overall response rates in the trial [15, 40]. A minimum number of patients per tumor type should be enrolled in order to properly perform the analysis [12]. It has also been highlighted that it is crucial to consider the tumor environment and co-mutations that may potentially contribute to treatment resistance [41, 42].

5 Limitations

First, for most of the studies, the benefit and risk data were presented as pooled results without reflecting a specific tumor type. Although in some cases the type of cancer with a response was reported, we were not able to correlate this with the number of patients evaluated. It was rarely reported exactly how many patients with each type of cancer were evaluated. For this reason, we do not present the results of the risk-benefit analysis by specific cancer type, but only by solid tumors, hematologic tumors, or a combination of the two. Furthermore, we did not consider stable disease as a measure of clinical benefit, although it may be regarded as an indicator of clinical benefit. Stable disease is a guideline for continuing treatment rather than a criterion for response. Moreover, it may reflect inherent characteristics of the tumor rather than disease activity and it is not generally used in regulatory approval (including accelerated approval) [43].

Second, we did not perform a subgroup analysis for benefit and risk outcomes based on the individual drugs or biomarkers tested because of the very high heterogeneity (85 different interventions or unique drug combinations and 67 unique biomarkers per 126 arms). Third, we did not statistically compare matched and non-matched studies because only 2 of 126 studies were non-matched and the others were matched. The first study evaluated cetuximab in patients without KRAS, NRAS, or BRAF mutations (TAPUR, NCT02693535) [44]. The second study evaluated perifosine monotherapy for recurrent gynecologic cancer without PIK3CA mutations (no NCT ID reported) [45]. In the non-match studies, participants did not respond to treatment, for both, ORR = 0. In one study, there was no treatment-related death, and for the other, information on deaths was not reported.

Finally, we present the results in terms of the number of study arms evaluated in 75 basket trials rather than the number of clinical trials. The number of 126 studies included in the analysis consists of 66 arms, each representing one trial, and 60 arms that are part of multi-arm trials, corresponding to nine BCTs (i.e., more than one arm was included for a single trial). We adopted a similar strategy when analyzing results for umbrella-type clinical trials [11]. Thus, our results show a comparison between arms of BCTs rather than individual trials.

6 Conclusions

Our findings have implications for ethics review, data monitoring, and communication in the context of novel clinical trial designs that adapt the precision medicine approach. We provided an estimate of risk and benefit rates for participants in BCTs, which recruit patients with different cancer locations based on the presence of specific biomarkers. Although BCTs are promising, we have found that nearly four out of five people who participate in a trial did not respond partially or completely to treatment and one in 135 died because of drug toxicity. In addition, nearly one third experienced grade 3–4 treatment-related AEs. It is therefore important that patients recruited into these trials are properly informed about the anticipated benefits and risks. While we acknowledge that our analysis does not cover all aspects related to benefits and risks, we note that efforts should be made to increase the reporting of data that allows for such assessments.

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Declarations

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Availability of data and material Data used for our analysis are publicly available on the Open Science Framework website (https://osf.io/w4ke9/). Additional data are available upon request.

Code availability Not applicable.

Author contributions Conceptualization: KK, KS, MW. Investigation (data collection): KK, KS, LZ, AW, TK, UBK. Methodology: KK, KS, SVW, MW. Data curation: KK, KS, LZ, AW, TK, UBK. Formal analysis: KK, MP. Funding acquisition: KK, KS, MW. Project administration: KK, KS, MW. Resources: KK, KS. Supervision: SVW, MW. Visualization: KK. Software: KK, KS, MP, MW. Validation: KK, KS. Writing, original draft: KK, KS. Writing, review and editing: all authors.

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7.4 Publikacja P4

PLOS ONE

RESEARCH ARTICLE

Seamless trials in oncology: A cross-sectional analysis of characteristics and reporting

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Abstract

Objectives

Seamless clinical trials have received much attention as a possible way to expedite drug development. The growing importance of seamless design can be seen in oncology research, especially in the early stages of drug development. Our objective is to examine the basic characteristics of seamless early-phase oncology trials registered on the ClinicalTrials.gov database and to determine their results reporting rates. We also aim to identify factors associated with results reporting.

Methods

Cross-sectional study. We defined seamless early-phase trials as either those registered as Phase 1/2 or Phase 1 with planned expansion cohort(s). Using the ClinicalTrials.gov registry, we searched for interventional cancer clinical trials with primary completion date (PCD) between 2016 and 2020. After trial selection, we performed manual data extraction based on the trial record description and the results posted in the trial registry. We used logistic regression to search for predictors of results reporting. Protocol: https://osf.io/m346x/.

Results

We included 1051 seamless early-phase oncology trials reported as completed (PCD) between 2016 and 2020. We provided descriptive statistics including the number of patients enrolled, study start date, primary completion date, funding, type of intervention, cancer type, design details, type of endpoints, recruitment regions, and number of trial sites. Overall, only 34.7% trials reported results on ClinicalTrials.gov. The results reporting rates for 24 months was 24.0%. The overall reporting rate for Phase 1/2 studies was over three times higher than for seamless Phase 1.

Conclusions

Our study provides cross-sectional data on seamless early-phase oncology trials registered on ClinicalTrials.gov. We highlight the challenges of the evolving clinical trial design

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landscape and the problem of missing results in the seamless design context, which raises serious ethical concerns. Efforts should be made to adapt the functionality of the ClinicalTrials.gov database to emerging clinical trial models.

Introduction

In recent years, the landscape for conducting clinical trials has evolved. New clinical trial design solutions are emerging with promise of greater flexibility and speed in the drug development process [1,2]. Seamless clinical trials, a type of adaptive clinical trial design, are one such solution [3].

Seamless trials often combine two distinct phases of drug development, allowing for the concurrent assessment of objectives traditionally assessed in separate trials [1]. In the traditional approach, the clinical trials of a drug are conducted sequentially in separate trials from Phase 1 to Phase 3 prior to marketing approval. Phase 1 trials focus primarily on evaluating initial safety and dose tolerance. Phase 2 trials aim to analyze preliminary efficacy. Phase 3 trials evaluate the investigational drug's comparative benefits. Seamless designs may adopt a Phase 1/2 trial format, concurrently addressing safety and efficacy as one trial. Similarly, a Phase 2 and a Phase 3 trial may be combined into a seamless Phase 2/3 trial. By merging phases and moving seamlessly from one phase to another, the gap between initiating a separate phase (as in the traditional mode) is eliminated [3–5].

Seamless clinical trials may also refer to Phase 1 trials intending to include an expansion cohort(s) after completion of the dose escalation component [6–9]. Additional cohorts of patients may be seamlessly added to the Phase 1 trial to further evaluate the drug within the same trial. As a result, a Phase 1 study with expansion cohorts typically enrolls a larger number of participants. It is not primarily limited to analyzing the safety and determining the tolerated dose of the therapy being tested [10]. It also may assess other aspects typically associated with Phase 2 trials, such as preliminary efficacy [8].

Clinical trials using the "seamless design" methodology are used across a range of medical disciplines, including for example cardiology, pulmonology, vaccine development [1,11,12]. Seamless design was also used in clinical trials conducted during the global pandemic caused by the SARS-CoV-2 virus [13,14]. Nevertheless, the increasing significance of seamless design is particularly evident in the context of oncology research [4,5,15,16]. Advances in oncology drug development, including precision medicine approaches and novel targeted and immunotherapies, have stimulated the need to detect antitumor activity as early as possible [7]. The increased use of seamless design in the early stages of new anticancer drug development is particularly striking. The purpose is to enable the selection of the most promising therapies at an early stage, which eventually may result in earlier access to treatment for cancer patients [3,4,8,15,17].

Our objective is to examine the basic characteristics of seamless early-phase oncology trials that are registered on the ClinicalTrials.gov database. We aim to determine their results reporting rates and identify factors associated with faster results reporting.

Methods

This cross-sectional meta-research study follows a pre-specified protocol available on the Open Science Framework (OSF) website (https://osf.io/m346x/) [18]. The study relies on publicly accessible data and follows the Strengthening the Reporting of Observational studies in

Epidemiology (STROBE) reporting guideline for cross-sectional studies (see S1 Table) [19]. An overview of the methods is presented in Fig 1.

Sample and trial selection

We identified our sample on ClinicalTrials.gov. We chose this platform because it is a well-known clinical trial registry and a repository of clinical trial data from around the world. It is also a relational database that is used to conduct scientific research on the design of clinical trials [20]. We defined seamless early-phase trials as either those registered as Phase 1/2 or Phase 1 with planned expansion cohort(s). Using the advanced search function available on the ClinicalTrials.gov registry, we searched for interventional cancer clinical trials with primary completion date (PCD) between 2016 and 2020 that were registered as Phase 1 and Phase 1/2 trials. We chose the time range for two reasons: to obtain a sample of reasonable and feasible size, and to give each trial at least two years after the primary completion date to submit summary results to the ClinicalTrials.gov database. We automatically downloaded the dataset as a CSV file on 01/03/2023. We used the following search string to generate the sample: Completed Studies | Interventional Studies | Cancer | Phase 1, 2 | Primary completion from 01/01/2016 to 12/31/2020. See more details about search strategy in S2 Table.

During trial selection, we automatically excluded trials registered as Phase 2 and Phase 2/3 from our dataset. Then, we performed manual assessment of trial eligibility, which required evaluation of the full trial record on the ClinicalTrials.gov registry. We searched for trials testing drugs and biologics for antitumor activity. Both adult and pediatric studies evaluating both solid tumors and hematologic malignancies were included. We conducted additional assessments for eligible Phase 1 trials. Our aim was to specifically include Phase 1 trials meeting the criteria for a seamless design. To ensure this, we examined whether the descriptions of these trials mentioned the expansion cohort directly. In the absence of direct information on the expansion cohort, we checked the study description for information on an additional group of patients recruited into the study after the end of the dose-escalation component. If neither criterion was met, we excluded the Phase 1 study from further analysis. The full inclusion and exclusion criteria can be found in the protocol [18].

Prior to manual assessment, each reviewer received training and conducted a pilot. During the manual trial selection process, each trial record was assessed independently by two reviewers (KK assessed all trial records, and the second reviewer was KS, PB, or AW). Disagreements were resolved by discussion and, if necessary, by a referee (MW).

Data collection

We created and piloted an extraction form [18] (see S1 File). For each of the included trials, we performed a double-checked manual extraction of the data. Disagreements were reconciled through discussion and, if necessary, the involvement of an arbiter. We extracted some of the data directly from the dataset downloaded from ClinicalTrials.gov. This included the start and end dates of the study, the age of the study participants, the number of enrolled patients, the type of funder, whether the results were reported, and, if so, when they were first reported.

We assessed other variables using data from the ClinicalTrials.gov website (online access). Based on the record description, we determined the design details (randomization, masking, interventional model), the type of intervention, the number of drugs evaluated, the type of cancer, and the number and location of study sites. We also confirmed whether the trial description reported the trial phase consistently. This involved searching for any discrepancies in phase reporting across different sections of the study record on ClinicalTrials.gov. An example of a discrepancy was a trial registered as Phase 1/2, yet only Phase 1 was mentioned in the

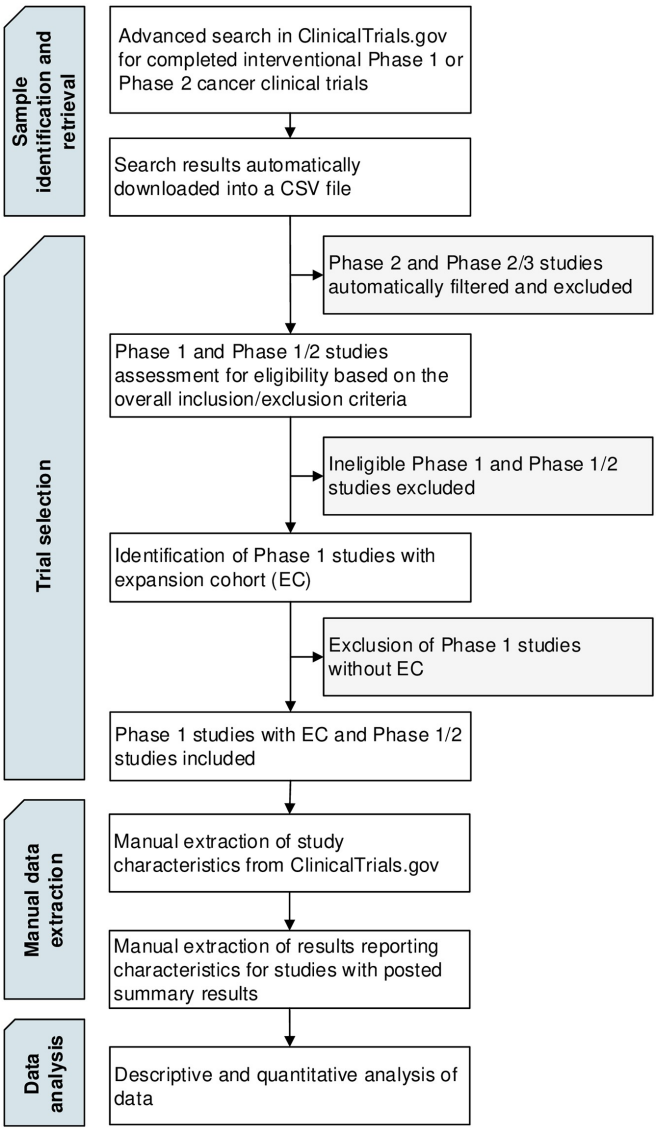

Fig 1. Method overview.

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record description. We also examined whether the study record reported the presence of each seamless trial stage. In this analysis, "trial stage" refers to Phase 1 or Phase 2 for Phase 1/2 trials, and to the stage preceding the enrollment of expansion cohort(s) and the expansion cohort(s) themselves for seamless Phase 1 trials.

In addition, we verified whether included Phase 1/2 trials met the definition of seamless Phase 1 trials. For those trials that directly mentioned "expansion cohort", we checked where this phrase was mentioned in the study record within the specific sections on ClinicalTrials.gov. This was a sequential process. First, we checked the Title section, then the other elements of the Study Overview section (i.e. Brief and Detailed Description), the Arms and Interventions, and the Participation Criteria.

For all studies in our sample, we assessed the types of endpoints. We checked the number of studies that reported the following endpoints: dose-limiting toxicities (DLTs)/maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), treatment-related adverse events (TRAEs), progression-free survival (PFS), overall survival (OS), response rates (RR) (e.g. overall response rate) and pharmacokinetic measures. Synonymous terms referring to these endpoints were also considered. We checked if the primary endpoints were separately reported for each seamless trial stage.

For studies with reported results, we assessed the characteristics of the results reporting. Results on ClinicalTrials.gov are usually presented as a separate table for participant characteristics and outcome measures. Our goal was to explore whether the data for each trial stage were reported separately or together. To classify a Phase 1/2 trial as one with separately reported data for each trial stage, results should be reported separately for Phase 1 and Phase 2. Likewise, for a seamless Phase 1 study, results should be reported separately for the stage preceding the initiation of the expansion cohort(s) and for the expansion cohort stage.

As ClinicalTrials.gov is a continuously updated database, the reference point for data extraction was the version of the record in effect at the time of the data search and download. If the date of the last record update was after 01/03/2023, we extracted data from the historical version of the trial record. We present the details about trial characteristics categorization in S3 Table.

Statistical analysis and tools

We used Cohen's kappa to calculate the inter-rater agreement between the reviewers for the study selection. We presented the descriptive statistics for the both the entire sample of seamless early-phase oncology trials and separately for each phase. We reported counts and percentages for categorical variables. We assessed trial duration as time from study start date to primary completion date. We calculated the time to results reporting as the time from the primary completion date to the date when the results were first reported. We described the time to results reporting by median with interquartile range (IQR). We reported on rates of trials that posted the results on ClinicalTrials.gov (overall and within 24 months since primary completion date).

We used the chi-square test or Exact Fisher test to examine the differences in results reporting between trials characteristics. To compare time to reporting results between trial characteristics, we used Mann-Whitney U test or Kruskal-Wallis test. We performed the multivariable logistic regression analysis to find the independent predictors of reporting results within two years. As we considered clinical trials with a primary completion date between 2016–2020, we evaluated the predictors with respect to two years (24 months), so that each trial had at least two years to report results. We chose 24 months for our analysis with reference to the World Health Organization's "Joint statement on public disclosure of results from clinical trials" [21].

This statement indicates that the primary results of a clinical trial should be reported in a registry within 12 months and published in a peer-reviewed journal within 12 months. Given the expected limited number of clinical trials that had reported results within the 12-month window, we decided to perform our statistical analysis in the 24-month window. All of the characteristics that were statistically significant in the univariable analysis were included in the multivariable model. Then backward elimination method was applied ($P<0.1$). We presented the results of regression model as odds ratio (OR) with 95% confidence interval (CI). We examined time to results reporting using Kaplan-Meier curves and compared using the log-rank test. For the study not reporting results, we censored the timeline on March 1, 2023. We performed analysis using Microsoft Excel and IBM SPSS Statistics for Windows, Version 28.0. (2021) Armonk, NY: IBM Corp. For statistical inference, N/R (not reported) was treated as missing data. All tests were 2-sided, and P-value less than 0.05 was considered statistically significant.

Results

Trial characteristics

We included 1051 early-phase seamless oncology trials reported as completed (PCD) between 2016 and 2020, including 562 (53.5%) seamless Phase 1 and 489 (46.5%) trials registered as Phase 1/2 (see S1 Fig for flow diagram). The inter-rater agreement (Cohen's kappa) between the reviewers during the trial selection was 0.78 (95% CI: 0.75–0.80). The characteristics of all included trials are presented in Table 1 and S4 Table, which present the characteristics of seamless Phase 1 and Phase 1/2 trials separately). The median number of enrolled patients was 45 (IQR: 25–85). Median trial duration was 3.8 (IQR: 2.7–5.3) years. Of the 1051 studies, 813 (77.4%) were at least partially industry funded, 987 (93.9%) were adult studies, 922 (87.7%) were non-randomized and 733 (69.7%) were multi-site. Almost half of the trials (512, 48.7%) were conducted in North America and 476 (45.3%) were conducted exclusively in the United States.

Most trials evaluated multiple agents (654, 62.2%). We found that 238 (22.6%) trials evaluated immunotherapies, 263 (25.0%) targeted therapies, 67 (6.4%) cytotoxic therapies. Other types of therapy were reported in 25 (2.4%) trials and 458 (43.6%) trials evaluated combinations of at least two of the above. The majority of trials involved solid cancers (752, 71.6%). Over half (530, 50.4%) evaluated more than one type of cancer. The most common types of cancer mentioned in study descriptions on ClinicalTrials.gov include lung cancer, breast cancer, lymphoma, leukemia, ovarian cancer, and colorectal cancer. These indications were mentioned in at least 10% of the assessed trials. See S5 Table for more details.

We found that the description of the study was consistent with phase registration in the case of 1010 (96.1%) trials. The study record reported the presence of each seamless trial stage in the case of 903 (85.9%) trials. Of the 489 of Phase 1/2 trials, 301 (61.6%) met the criteria for Phase 1 with expansion cohort(s). The expansion cohort was directly mentioned in 665/1051 (63.3%) trials (i.e. 518/562 (92.2%) for Phase 1 and 147/489 (30.1%) for Phase 1/2). Of these, only 92/665 (13.8%) mentioned expansion cohort(s) in the "Title" and more than half (376/665, 56.5%) in "Brief and Detailed Description". See S6 Table for more details.

Of the endpoints evaluated, MTDs or DLTs occurred in 747/1051 (71.1%) studies, and RP2D in 168 (16.0%). PFS, OS and RR were reported in 518 (49.3%), 388 (36.9%) and 856 (81.4%) trials, respectively. TRAEs occurred in 142 (13.5%) studies. Pharmacokinetic measures were identified in 559 (53.2%) studies. Only 189 (18.0%) studies reported primary endpoints by seamless trial stage. We found that MTD or DLTs, RP2D, and TRAEs were mainly reported as primary endpoints, while OS, PFS, RR, and pharmacokinetic measures were reported as

Table 1. Characteristics of oncology seamless early-phase clinical trials completed between 2016 and 2020 registered on ClinicalTrials.gov.

Characteristic[a]	N (%)
Number of trials	1051 (100%)
Phase	
Phase 1	562 (53.5%)
Phase 1/2	489 (46.5%)
Enrolled participants	
1–50	594 (56.5%)
51–100	246 (23.4%)
101–150	105 (10.0%)
151–200	48 (4.6%)
>200	58 (5.5%)
Study start date	
2013–2014	325 (30.9%)
2015–2016	301 (28.6%)
2011–2012	188 (17.9%)
2017–2018	138 (13.1%)
≤2010	91 (8.7%)
2019–2020	8 (0.8%)
Primary completion date	
2019	239 (22.7%)
2020	224 (21.3%)
2017	205 (19.5%)
2018	193 (18.4%)
2016	190 (18.1%)
Funder type	
Industry	596 (56.7%)
Non-industry	238 (22.6%)
Partially-industry	217 (20.6%)
Study population age[b]	
Adults	987 (93.9%)
Both	61 (5.8%)
Pediatric	3 (0.3%)
Type of intervention	
Mixed[c]	458 (43.6%)
Targeted therapy	263 (25.0%)
Immunotherapy	238 (22.6%)
Cytotoxic therapy	67 (6.4%)
Other	25 (2.4%)
Number of drugs evaluated in the study	
Multiple agents	654 (62.2%)
Single agent	397 (37.8%)
Type of cancer	
Solid	752 (71.6%)
Hematological	250 (23.8%)
Both	46 (4.4%)
Not reported	3 (0.3%)
Number of cancer types	

(*Continued*)

Table 1. (Continued)

Characteristic[a]	N (%)
Multiple	530 (50.4%)
Single	521 (49.6%)
Masking	
Open label	1032 (98.2%)
At least double-blind	15 (1.4%)
Single blind	1 (0.1%)
Not reported	3 (0.3%)
Randomization	
Non-randomized	922 (87.7%)
Partially randomized	56 (5.3%)
Randomized	55 (5.2%)
Not reported	18 (1.7%)
Interventional model	
Single group assignment	622 (59.2%)
Parallel assignment	268 (25.5%)
Sequential assignment	144 (13.7%)
Factorial assignment	5 (0.5%)
Cross-over assignment	3 (0.3%)
Not reported	9 (0.9%)
Number of trial's sites	
Multi-site	733 (69.7%)
Single-site	307 (29.2%)
Not reported	11 (1.0%)
Recruitment regions #1	
North America	512 (48.7%)
Mixed	254 (24.2%)
Europe	147 (14.0%)
Asia	112 (10.7%)
Australia	14 (1.3%)
South America	1 (0.1%)
Not reported	11 (1.0%)
Recruitment regions #2	
United States (US)	476 (45.3%)
Non-US	298 (28.4%)
Multicenter including US	266 (25.3%)
Not reported	11 (1.0%)

[a]The characteristics are presented in descending order of frequency, with the exception of the "not reported" category.

[b]The categorization was adopted directly from the ClinicalTrials.gov registry. We chose "Pediatrics" for the "Child" category or age under 18 (if the specific age range was reported). And "Adult" for the "Adult" and "Older Adult" categories and age over 18.

[c]The "Mixed" for "type of intervention" category encompasses combinations of at least two drugs from two distinct categories, including targeted therapy, immunotherapy, cytotoxic therapy, and other treatments.

US: United States.

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secondary endpoints. See S7 Table for details on the division into primary and secondary endpoints.

Rates of results reporting

With a median follow-up of 518 (IQR: 412–801) days, 365 of 1051 trials (34.7%) reported results on ClinicalTrials.gov. Two trials (0.5%) published results before their primary completion date. Overall, more than half (269/489, 55.0%) of the Phase 1/2 trials posted results on ClinicalTrials.gov, whereas less than one in five Phase 1 trials (96/562, 17.1%) did so. The overall reporting rate for Phase 1/2 studies was therefore more than three times higher than for seamless Phase 1 studies (see Table 2 and S2 Fig). The rate of results reported within 24 months was 24.0% for all trials, 10.7% for Phase 1 and 39.3% for Phase 1/2 (see Table 2). We present the time to results reporting for all trials in our sample in Fig 2 and separately for each phase in S2 Fig. For comparison of time to reporting results based on trial characteristics see S8 Table.

Characteristics of the results reports

We found that patient characteristics and outcome results were reported separately for each trial stage in 176/365 (48.2%) trials, reported together (not broken down by trial stage) in 145 trials (39.7%), and reported only for the first stage in 17 (4.7%) trials. In 27 (7.4%) trials, the results reporting was inconsistent for participants and outcomes (e.g. characteristics of participants were reported separately for each stage but together for the outcomes). Among the clinical trials with results separately reported, the median number of expansion cohort(s) or Phase 2 cohort(s) was 2 (IQR: 1–3). The median number of patients enrolled in all expansion/Phase 2 cohorts was 45 (IQR: 24–93).

Predictors of results reporting

We present the comparison of trials with results reported within 24 months in Table 2. A higher proportion of results reported within 24 months was associated with Phase 1/2 trials, US-led trials, trials with a later primary completion date, partially randomized trials, trials with larger recruitment targets, and trials evaluating multiple agents, hematologic cancers, and mixed population age.

In multivariable analysis (Table 3), we found five independent predictors of reporting results within 24 months. The odds of reporting (OR) were more than eight times higher for Phase 1/2 trials than for Phase 1 trials. We found that compared to solid tumors, hematologic malignancies had 1.5 times higher odds of reporting. Trials conducted in or involving the United States had 6.7 and 8 times higher odds of reporting, respectively, than non-US trials. The odds of reporting results were 1.58 times higher for trials recruiting more than 50 and fewer than 100 participants compared to trials recruiting 50 or fewer participants. The later the primary completion date of the trial, the greater the odds of results being reported on ClinicalTrials.gov (OR = 1.4).

Discussion

Seamless design is relatively new in clinical trials. This clinical trial model has gained popularity as a way to accelerate drug development. The interest in seamless design in oncology was sparked by the successful Phase 1 trials with expansion cohorts that led to accelerated approval of pembrolizumab in melanoma in less than 4 years in 2014 [4,5,15]. Currently, early phase dose-expansion cohort studies are an important type of study to support the Food and Drug Administration approval of targeted anticancer drugs [22].

Table 2. A comparative analysis of results reporting rates based on the characteristics of the trials.

Characteristic	Trials with results reported within 24 months		Trials with results reported (overall)	
	N (%)[a]	P-value	N (%)[a]	P-value
All trials	252 (24.0%)	Not applicable	365 (34.7)	Not applicable
Phase				
Phase 1	60 (10.7%)	<0.001	96 (17.1%)	<0.001
Phase 1/2	192 (39.3%)		269 (55.0%)	
Enrolled participants				
1–50	111 (18.7%)	<0.001	166 (27.9%)	<0.001
51–100	66 (26.8%)		95 (38.6%)	
101–150	38 (36.2%)		52 (49.5%)	
151–200	13 (27.1%)		18 (37.5%)	
>200	24 (41.4%)		34 (58.6%)	
Study start date				
≤2010	28 (30.8%)	0.036	41 (45.1%)	0.006
2011–2012	43 (22.9%)		74 (39.4%)	
2013–2014	68 (20.9%)		111 (34.2%)	
2015–2016	86 (28.6%)		106 (35.2%)	
2017–2018	24 (17.4%)		30 (21.7%)	
2019–2020	3 (37.5%)		3 (37.5%)	
Primary completion date				
2016	31 (16.3%)	<0.001	61 (32.1%)	0.706
2017	35 (17.1%)		71 (34.6%)	
2018	46 (23.8%)		71 (36.8%)	
2019	60 (25.1%)		78 (32.6%)	
2020	80 (35.7%)		84 (37.5%)	
Funder type				
Industry	135 (22.7%)	0.458	200 (33.6%)	0.623
Non-industry	59 (24.8%)		88 (37.0%)	
Partially-industry	58 (26.7%)		77 (35.5%)	
Study population age				
Adults	230 (23.3%)	0.006	334 (33.8%)	0.009
Pediatric	3 (100.0%)		3 (100.0%)	
Both	19 (31.1%)		28 (45.9%)	
Number of drugs evaluated in the study				
Single agent	69 (17.4%)	<0.001	101 (25.4%)	<0.001
Multiple agents	183 (28.0%)		264 (40.4%)	
Type of cancer				
Solid	167 (22.2%)	<0.001	252 (33.5%)	0.006
Hematological	80 (32.0%)		104 (41.6%)	
Both	5 (10.9%)		9 (19.6%)	
Number of cancer types				
Single	136 (26.1%)	0.109	207 (39.7%)	<0.001
Multiple	116 (21.9%)		158 (29.8%)	
Masking				
Open label	249 (24.1%)	1	354 (34.3%)	1
Single blind	0 (0.0%)		1 (100.0%)	
At least double-blind	3 (20.0%)		10 (66.7%)	
Randomization				

(*Continued*)

Table 2. (Continued)

Characteristic	Trials with results reported within 24 months		Trials with results reported (overall)	
	N (%)[a]	P-value	N (%)[a]	P-value
Non-randomized	212 (23.0%)	0.018	302 (32.8%)	<0.001
Partially randomized	22 (39.3%)		38 (67.9%)	
Randomized	11 (20.0%)		14 (25.5%)	
Number of trial's sites				
Single-site	64 (20.8%)	0.182	92 (30.0%)	0.05
Multi-site	181 (24.7%)		266 (36.3%)	
Location				
United States (US)	138 (29.0%)	<0.001	199 (41.8%)	<0.001
Multicenter including US	82 (30.8%)		115 (43.2%)	
Non-US	25 (8.4%)		44 (14.8%)	

[a]Percentages are calculated as the ratio of clinical trials with results to all trials within each trial characteristic category. For example, the reported percentage of 10.7% for Phase 1 trials in the "Trials with results reported within 24 months" column refers to the ratio of the number of Phase 1 trials with results reported within 24 months (60 trials) to the number of all Phase 1 trials (562 trials) in the cohort.

We used the chi-square or exact Fisher test to examine differences in results reporting by trial characteristics. P-value less than 0.05 was considered statistically significant.

The table does not include values for "not reported". For statistical inference, the variable "not reported" was treated as missing data.

US: United States.

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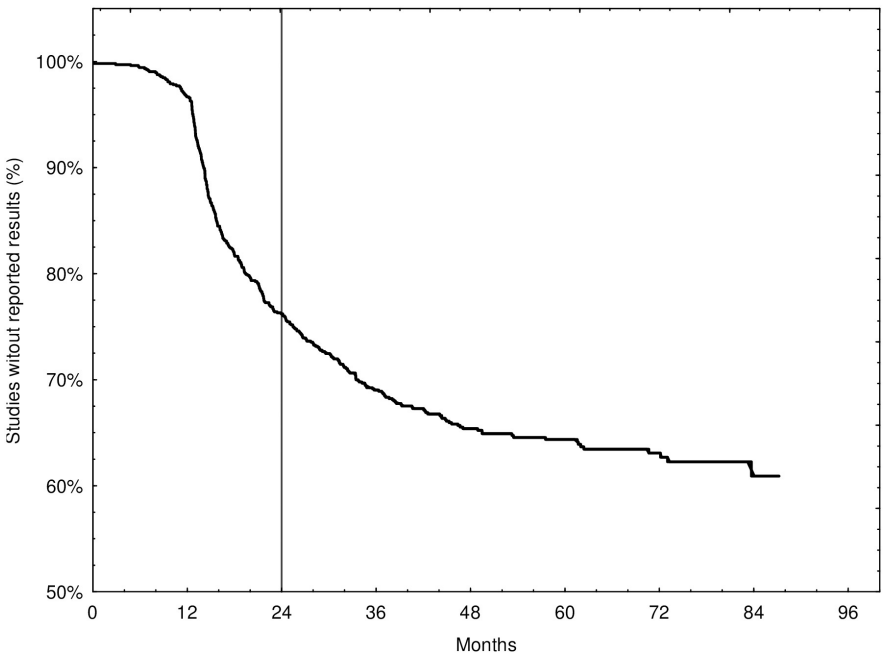

Fig 2. Kaplan-Meier curve for the cumulative probability of not reporting clinical trial results over time.

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Table 3. Independent predictors of results reporting within 24 months—Multivariable analysis.

Variable	OR	95% CI	P-value
Phase			
Phase 1	Ref		
Phase 1/2	8.361	(5.751–12.155)	<0.001
Type of cancer			
Solid	Ref		
Hematological	1.506	(1.035–2.190)	0.032
Both	0.396	(0.138–1.139)	0.086
Location			
Non-US	Ref		
US	6.731	4.124–10.985)	<0.001
Multicenter including US	8.051	(4.552–14.240)	<0.001
Enrolled participants			
1–50	Ref		
51–100	1.581	(1.044–2.394)	0.031
101–150	1.713	(0.976–3.007)	0.061
151–200	1.851	(0.833–4.114)	0.131
>200	1.534	(0.750–3.141)	0.242
Primary completion date (per year)	1.403	(1.239–1.589)	<0.001

In the multivariable model, the characteristics that were statistically significant in the univariable analysis were included (see Table 2, analysis for trials with results reported within 24 months) and the backward elimination method was applied ($P < 0.1$). US: United States. OR: odds ratio. CI: confidence interval.

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In our study, we provide a comprehensive evaluation of seamless early phase clinical trials in oncology based on ClinicalTrials.gov registry data. We found that among 1051 trials only around 35% reported results on ClinicalTrials.gov. We showed that more than half of the Phase 1/2 trials disseminated the results. In contrast, less than 20% of the seamless Phase 1 trials presented results. In comparison, another study that evaluated the reporting of results among all interventional oncology trials registered on ClinicalTrials.gov from 2007 through 2017 indicates that the results were posted on ClinicalTrials.gov for 22.9% (95% CI, 22.2%-23.7%) of the trials [23]. Our findings for seamless early-phase clinical trials in oncology are consistent with other reports and confirm the need for overall improvement in results reporting, particularly with regard to posting results to clinical trials registries [23–27]. While the issues described with reporting results on the ClinicalTrials.gov registry are not new, there are a number of points to be made about the data we collected.

Seamless design promises accelerated drug development but also raises ethical challenges. As registration and dissemination of Phase 1 trial results on ClinicalTrials.gov are optional, seamless early-phase trials tend to have lower transparency [5,28]. The low rate of results reporting from seamless trials revealed by our study heightens this concern. Inadequate reporting slows the generation of knowledge about tested substances, diminishing the potential of seamless trials for acceleration. This issue extends to other innovative clinical trial designs, such as basket and umbrella trials [29–32].

With the increasing use of adaptive clinical trial methods, improvements in the functionality of clinical trial registries are needed. Clinical trial registries, such as ClinicalTrials.gov, should be optimized to enable easy tracking of the entire trial process and to accommodate the complexity of novel trial designs [5,33]. Recently, a call for improvements in the registration

and reporting of results for master protocols was published [33]. A master protocol is a clinical trial design that allows the evaluation of multiple interventional hypotheses. It typically involves multiple sub-studies. This challenges established registry tools, as they only allow presentation of condensed details about trial characteristics [1,33]. Hence, the authors call for separate registration of each sub-study for greater transparency and accountability [33].

Other authors have also commented on specific challenges in reporting seamless clinical trials [4,5]. One of the highlighted problems is that registration records on ClinicalTrials.gov may not delineate the distinct cohorts of seamless trials [5]. Therefore, trial results may be available for the entire trial rather than specific seamless trial stages. This causes difficulty in accurately tracing the trial process. In our study, we provide evidence to support this hypothesis. We found that results per seamless trial stage were presented in only half of the trials with published results. In addition, although most trials reported on the presence of each seamless trial stage, finding specific details about them proved challenging. For example, we found that less than 20% of trials reported primary outcomes specifically for each trial stage. For trials that evaluated more than one therapy, it was unclear whether this applied to the entire trial or just part of it. It was also unclear how participants would be recruited, or whether they would participate in the entire study or only in a selected stage.

Moreover, improvements should be made to help distinguish traditional Phase 1 studies from Phase 1 studies that meet seamless design criteria. We propose that for each Phase 1 study it should be clearly stated whether it will include expansion cohorts. Such an additional field could appear in the study description. In addition, the trial description should reflect the type of seamless trial being conducted. There are two types of seamless designs: inferential and operational [1]. In an operationally seamless design, the time between two phases is eliminated, but the analysis of results is performed for separate stages. In contrast, an inferential seamless design combines data from both stages in the final analysis. Actions should be taken to improve the comprehensibility of the study and the clarity of the description in this regard.

Limitations

We have attempted to identify all eligible seamless clinical trials in our cohort. However, we acknowledge that our search strategy has some limitations. We used the term "cancer" to identify cancer clinical trials. We admit that this may have limited our sample with trials that used other terms e.g. neoplasm. Additionally, the ClinicalTrials.gov database underwent an interface change during the course of our study that affected both the description of certain elements in the clinical trial records and the functionality of the advanced clinical trial search tools. Moreover, there is a risk of some misclassification. The project relied on data reported on ClinicalTrials.gov, which varies widely in availability and accuracy. This data may be incomplete and may not have been updated since initial registration. Additionally, the evaluation of Phase 1 trials was hindered by the absence of clear information in the database indicating that the trial would follow a seamless design. Therefore, we applied a generous criterion by checking whether the trial description included information that there would be an expansion cohort or an additional group of patients after completion of the dose escalation stage. We also included clinical trials regardless of the planned number of enrolled participants. Our criterion differs from that used by other researchers [4]. They included in their analysis those seamless trials that had enrolled at least 100 participants. A significant number of the trials included in our analysis were conducted in North America. This regional concentration may limit the generalizability of the findings. Furthermore, we limited our search for clinical trial results to those reported on ClinicalTrials.gov. Results may have been reported elsewhere, potentially biasing the numbers. Further analyses should be conducted to assess the availability of results in other sources,

including journal publications or other clinical trial registries (due to the phenomenon of cross-registration of the same trial in different registries, especially for non-North American trials).

Conclusions

Our study provides cross-sectional data on seamless early-phase oncology trials registered on the ClinicalTrials.gov registry. We highlighted the challenges posed by the evolving landscape of clinical trial design and the issue of missing results within the context of seamless trial design. With a median follow-up of 518 days, only 34.7% trials reported results on ClinicalTrials.gov. The overall reporting rate for Phase 1/2 studies was more than three times higher than for seamless Phase 1 studies. Efforts should be made to adapt the functionality of the ClinicalTrials.gov database to emerging clinical trial models. One of the overarching issues to be addressed in implementing a seamless design is effectively capturing the nature of staging and sequential cohorts, both in describing trial characteristics and in presenting results.

Supporting information

S1 Fig. Flow diagram for identification of seamless early-phase oncology trials.
(DOCX)

S2 Fig. Kaplan-Meier curve for the cumulative probability of not reporting clinical trial results over time—Comparison between seamless Phase 1 and Phase ½.
(DOCX)

S1 File. Data extraction form.
(XLSX)

S1 Table. STROBE statement—Checklist of items that should be included in reports of cross-sectional studies.
(DOCX)

S2 Table. ClinicalTrials.gov search parameters.
(DOCX)

S3 Table. Details on data categorization for trial characteristics.
(DOCX)

S4 Table. Characteristics of a seamless Phase 1 study and a Phase 1/2 study.
(DOCX)

S5 Table. Type of cancer.
(DOCX)

S6 Table. Details on studies with an expansion cohort directly mentioned.
(DOCX)

S7 Table. Characteristics of the endpoints.
(DOCX)

S8 Table. Comparison of time to reporting results based on trial characteristics.
(DOCX)

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