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The impact of research waste on the scientific validity and integrity of clinical trials[1]

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Despite advancements in medicine and research methodology as well as enormous financial investments, many clinical trials do not provide the expected results, which is to deliver new, safe and effective drugs on the market. While this may stem from the poor performance of the tested treatment, many failures in clinical trials may be due to flaws in their design, conduct, and data analysis. Together with misconduct, non-reporting, and publication bias, this amounts to research waste that has a negative impact on the scientific validity and integrity of clinical trials. These flaws may endanger the wellbeing of trial participants. This article provides an overview of different sources of research waste in clinical trials, with a special focus on early phase trials that enrol paediatric participants. Finally, hallmarks of wasteful trials identifiable at the stage of Ethics Committee assessment are discussed. The article proposes solutions that may reduce the negative effects of research waste, strengthening the scientific validity and integrity of new clinical trials.

Keywords: bioethics, early-phase clinical trials, pediatric participants, scientific validity and integrity, social value.

1. Background

Clinical trials that enrol human subjects are essential for continued progress in medicine as they allow for the development of new therapies. Conducting biomedical and clinical trials is associated with enormous costs – the annual global spending on biomedical research reached US$ 240 billion in 2010 (Chalmers et al., 2014). Many trials, however, do not provide the expected results and do not meet their primary aim, which is to bring new, safe and effective drugs to market. The development of any pharmaceutical agents intended for human use involves undertaking clinical trials. These are generally divided into phases from 1 to 4. The initial phase 1 trials are designed to estimate tolerability, pharmacokinetics and pharmacodynamics of a potential drug candidate. This typically involves testing the bioavailability and distribution of a substance in the body, as well as finding the maximum

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tolerated dose that is appropriate for further testing and ultimate use in clinical practice. Some phase 1 trials are called "first-in-human" as they are the first instance of the tested substance being used in human beings. They also most commonly involve healthy volunteers but when the tested treatment is particularly toxic, they may involve actual sick patients. This is true, for example, in the case of phase 1 trials in oncology. Later phase 2 and 3 trials, on the other hand, are intended to be confirmatory in nature. They are generally larger, longer and include the "target population" – patients similar to those who would be using the investigational drug in the future. These trials test the safety and effectiveness of the treatment used in the way it would be in clinical practice. Sometimes Phase 4 trials are performed after a pharmaceutical agent has obtained marketing authorization – they intend to provide "real-world" data on its use in a clinical setting (European Medicines Agency, 1998).

There seems to be a high rate of attrition during the process of clinical development. It has been estimated that approximately 90% of potential drugs that enter early stages of development are not ultimately approved for human use (DiMasi, Grabowski, and Hansen, 2016; Hay et al., 2014; London and Kimmelman, 2015). A recent systematic review looked at phase 1 paediatric cancer trials. The review shows that only 5% of trials led to drugs being registered for paediatric use in cancer therapy (Wasylewski et al., 2020). The average likelihood of approval for a substance that has reached phase 3 of clinical trials is around 50%, even less in such fields as neurology or oncology. Even approved therapies often offer only minor improvement in efficacy and safety when compared to already existing treatment (Hey and Kimmelman, 2015). While many failures in clinical trials are due to poor performance of the tested treatment itself, some trials fail or their results are unusable due to various avoidable flaws and shortcomings in their design, conduct and data analysis. This can be further compounded by other factors, such as misconduct, lack of proper oversight as well as publication bias and non-reporting of trial results. All these factors are now being collectively labelled as "research waste" (Chalmers et al., 2014; Chalmers and Glasziou, 2009; Chan et al., 2014; Ioannidis et al., 2014; Salman et al., 2014). Despite enormous advancements in the methodology of clinical trials, research waste remains a pressing issue for international bioethics. This is not only a case of inefficient research – many participants enrol in trials hoping that their involvement will help advance biomedical science. Trials that are badly designed, conducted and reported may prevent reaching that goal, therefore making it a serious breach of public trust, as well as research ethics (Zarin, Goodman, and Kimmelman, 2019). To be considered ethical, clinical research needs to conform with the principles of scientific validity and integrity. Scientifically valid research must adhere to rigorous methodology – research that is scientifically unsound is considered unethical, as it may expose patients to risk without generating meaningful results, benefits or knowledge (Council for International Organizations of Medical Sciences (CIOMS, 2016; Emanuel, Wendler, and Grady, 2000). Similarly, integrity of research means that it is conducted accurately and efficiently, while the results are interpreted honestly and without any bias (University of Bath, 2019; U.S. Department of Health and Human Services National Institutes of Health, 2019). The occurrence of research waste is contrary to those principles. This means that the scientific reliability and integrity of research must be constantly improved in order to ensure that trials have the greatest possible impact on medical knowledge and trial participants are protected from avoidable harm. The following article provides an overview of different sources of research waste in clinical trials with human subjects. It also describes the features of proposed research that should be considered in order to minimize research waste and increase the social value of new clinical trials.

2. Research waste in clinical trials

Research waste can occur at every stage of a clinical trial, from its inception and design, all the way through implementation and reporting. In an article published in 2009 in Lancet, Chalmers and Glasziou pointed out that the most prominent sources of waste are: irrelevant research questions, inappropriate design and methodology or a research report that is either biased or unavailable (Chalmers and Glasziou, 2009). They also estimate that the cumulative effects of those errors lead to wasting about 85% of total research investment (Chalmers and Glasziou, 2009). The issue of research waste was further elaborated in a special issue of Lancet in 2014, where several researchers described various factors that contribute to waste (Chalmers et al., 2014; Chan et al., 2014; Glasziou et al., 2014; Ioannidis et al., 2014; Salman et al., 2014). Since then, other authors have also been providing their views on the issue. Zarin et al., for example, define features that make trials uninformative and therefore wasteful (Zarin et al., 2019). Such trials cannot achieve their broad objective, which is the advancement of medical science. Zarin and colleagues identify certain features that any given trial needs to have if it hopes to be informative:

scientific, medical or policy importance – hypothesis addressing an important and unresolved question;
adequate design that makes the trial likely to provide meaningful results;
feasibility – reasonable anticipation that the study could recruit enough participants to provide informative results;
integrity – the trial is performed and the results are analyzed in a scientifically valid manner;
the study is likely to report its results in a timely manner, completely and accurately (Zarin et al., 2019).

Every type of clinical or pre-clinical biomedical research is susceptible to these kinds of errors, but early phase clinical trials (such as phase 1 and 2) are especially vulnerable given their first-in-human and exploratory nature. Their underlying rationale not yet fully developed, they may be prone to waste-generating errors in design and methodology. It should be noted that research waste can also occur in non-commercial trials, e.g. academic or investigator-initiated trials. These may be both interventional and non-interventional trials – the latter ones may be especially susceptible to waste-generating factors. For example, in Poland, non-interventional (or observational) trials are not required by law to be scrutinized by independent review bodies, such as Ethics Committees[2] (Ustawa o Zawodach Lekarza i Lekarza Dentysty, 1996), leaving them open to potential errors and biases. An independent review of observational studies is, however, recommended by international guidelines (World Medical Association Declaration of Helsinki, 2013; CIOMS 2016). This article focuses on research waste in commercial clinical trials, which are mainly focused on the development of new drugs or interventions. The issues specific to non-commercial trials are not discussed in detail, many of them, however, remain relevant.

Research waste is fast becoming a huge ethical concern. On the most basic level, it undermines the spirit of informed consent – a crucial requirement of all interventional studies that

[2] These panels or boards are tasked with reviewing and approving proposed biomedical research, including clinical trials. In the European setting, they are known as Ethics Committees (in Polish: *Komisje Bioetyczne*), in the USA, they are called Institutional Review Boards

involve human subjects (Czarkowski and Różyńska, 2008). When patients and volunteers agree to participate in trials, part of their motivation may be to contribute to medical progress. However, in the case of wasteful, uninformative trials, achieving this goal may be unlikely. Additionally, when patients enrol in a trial, they are not only subject to potential clinical benefit that might come from these unproven interventions, they are also at risk of unexpected adverse reactions. The same methodological and design factors that contribute to unreliable or unusable trial results may lead to lethal consequences for trial participants. Such was the case of a phase 1 trial of BIA-10-2474 (Wasylewski, 2017). This first-in-human trial enrolled healthy volunteers and was designed to test the pharmacokinetics of increasing doses of a substance that would be a potential drug in the treatment of various conditions. One of the subjects died due to adverse reactions to the tested compound, four others experienced serious neurological impairment. In the aftermath of this crisis, it became apparent that the trial itself was badly designed. The dose intervals tested in the trial were too wide, thus allowing for adverse reactions to manifest themselves unexpectedly and with full severity in the higher dose ranges, while they were non-apparent in lower dosages. It also appears that BIA-10-2474 was administered to every volunteer simultaneously. While giving the substance to one patient at a time would probably not have saved the life of the first participant, it would have ensured that the four subsequent patients would not have suffered from adverse reactions. The trial could have simply been stopped before more patients were administered the drug. Such an approach is called sentinel dosing. Furthermore, it is possible that the phase 1 trial in question should not have started at all, as the sponsor had reports of fatal toxicity from previous preclinical animal trials. It is unclear if or why the trial sponsor chose to disregard those data (Butler and Callaway, 2016; Fitzgerald, 2016). As evidenced by the BIA-10-2474 example, avoidable flaws and shortcomings in trial design and reporting increase the risk for patients currently undergoing trials. The occurrence of publication bias (i.e. not reporting some or all of completed clinical research) does the same for future patients. This was the case of another phase 1 trial, this time for a compound called TGN 1412. It led to a spectacular failure during first-in-human trials, which could have been prevented if relevant data from previous preclinical trials were available. Those trials had been previously conducted, but their lacklustre results went unpublished for many years and only became available after the tragic TGN incident (St. Clair, 2008). It is interesting to note that the case of the TGN trial led the European Medicines Agency to formulate guidelines for first-in-human and early clinical trials. These guidelines were revised in 2017 to give guidance on the aforementioned sentinel dosing, as well as on staggering subjects – a practice of maintaining a specified follow-up interval between the administration of a product to one subject or group of subjects and the administration to the next subject or group (Breithaupt-Grögler et al., 2019; European Medicines Agency, 2017).

2.1. Research waste in paediatric clinical trials

As covered in the previous paragraph, the consequences of research waste may be especially dire when a trial involves human subjects. There is consensus that trial participants always need to be protected from harm. This led to the formulation of regulations and recommendations to ensure that clinical research either poses only minimal risk for its subjects or offers them some form of direct benefit. If the risk cannot be sufficiently minimized, it has to be at least outweighed by direct or indirect benefit that comes from the study (Council for International Organizations of Medical Sciences (CIOMS), 2016; European Parliament and Council, 2014; Food and Drug Administration, 2019; World Medical Association Declaration of Helsinki,

2013). When a certain population of trial participants is considered particularly vulnerable, additional safeguards are put in place to ensure their well-being. This is true, for example, in the case of children that take part in clinical trials (Food and Drug Administration, 2019).

Even despite strict regulation and assessment associated with paediatric clinical trials, they are prone to the same waste generating factors as adult trials. A systematic review from 2016 assessed treatment response in a cohort of paired phase 1 and 2 paediatric oncology trials. It showed that many phase 2 in this field are started despite the fact that previous phase 1 trials showed little scientific reason to do so. The researchers found that 13 out of 35 analysed phase 2 studies were undertaken despite the objective response rate of 0% in a previous phase 1 trial. Only one of those phase 2 trials had what was judged to be a "positive conclusion". None exceeded the objective response rate of 15% (Yeh, Huang, and Cohen, 2016).

Another possible indicator of research waste in phase 1 clinical trials may be the inclusion of many different types of cancer in one study. The underlying rationale could be that researchers hoped that the treatment would prove effective in at least some of the included malignancies. This may mean that trials which cast a wider net and enrol patients with different types of malignancies generally involve less researched and developed drugs. In turn, this means the overall response to treatment in those trials would be lower than in trials that test one or few malignancies. A 2018 systematic review of paediatric phase 1 cancer trials found that most of them (62.9%) studied more than four types of malignancies, with only 12.4% of the trials studying only one malignancy. Further analysis showed that patients in trials testing fewer types of malignancies were more likely to have a response to treatment. The rate of objective response observed in trials testing up to three malignancies at the same time was approximately 15%, while in trials with four or more different malignancies, it was around 3% (Waligora et al., 2018). This may mean that there is a need to better assess whether the trial hypothesis is robust enough – adequately researched and based on animal and tissue models. Performing trials without a strong biological rationale – especially in paediatric oncology – seems inefficient. Another issue found by the review was the low quality of reporting, specifically for toxicity data. For example, in more than 58% of the studies, there was no explicit information about treatment related deaths (Waligora et al., 2018). Similar problems have been reported for paediatric studies elsewhere (Pica and Bourgeois, 2016). It seems that despite rigorous regulations and scrutiny from Ethics Committees, a lot of paediatric research based on flawed rationale is being performed.

3. The impact of waste on the social value of clinical trials

Most regulations and recommendations recognize that apart from providing some form of direct benefit for the participant, clinical trials should be able to benefit a wider population of current and future patients. This benefit is called "the social value" (Council for International Organizations of Medical Sciences (CIOMS, 2016; Habets, van Delden, and Bredenoord, 2014; Wendler and Rid, 2017). There is a general understanding that this value is the potential for generating and collecting data that may be used to improve health, although to date several sources have proposed their own systems of defining and quantifying social value in different types of clinical research (Casarett, Karlawish, and Moreno, 2002; Kimmelman, 2009). The CIOMS guidelines, for example, recognize that the social value of a study (the importance of the information a study can produce) is different from its scientific value – the ability to produce reliable and valid data. The guidelines agree that the requirement of being able to provide social

value together with a favourable risk/benefit balance is an essential prerequisite of any clinical trial involving humans. To satisfy that requirement, all the parties involved in clinical trials must ensure that such studies are "scientifically sound, build on an adequate prior knowledge base, and are likely to generate valuable information" (CIOMS, 2016). The importance of providing social value is even higher in early clinical trials (such as phase 1 or 1/2). These studies usually do not aim to inform clinical practice directly. Their usual goals and methodology (testing toxicity, pharmacokinetics and pharmacodynamics, mainly in healthy volunteers) often do not offer any prospect of realistic benefit to participants.

The social value of any given study may be diminished by an accumulation of factors that lead to research waste. Errors in rationale, design and implementation of a trial may lower its potential value, making otherwise promising drug candidates fall out of the development pipeline – substances that in different circumstances could yield favourable results. This is especially relevant at early stages of clinical development, where the rate of failure is the highest. Making it even higher by allowing bad trials to proceed is financially unviable and puts participants and patients at risk. The potential social value of a trial may also be completely negated by unavailable results. If the medical and scientific community cannot access the results of a trial – be they positive or negative – such a trial has no chance of influencing biomedical research or clinical practice in any way.

4. How to minimize research waste and increase its social value?

The responsibility of approving planned clinical trials rests upon the Ethics Committees. In many countries, especially in the European Union, this responsibility is shared with specialized national entities: competent authorities tasked with the assessment and monitoring of clinical trials, as detailed in the upcoming regulation (European Parliament and Council, 2001, 2014). This approval is mainly done by checking whether the risk/benefit ratio meets the minimal requirements, and patients or volunteers are adequately informed before giving consent to participate in a trial (Clapp, Gleason, and Joffe, 2017). While this is admittedly of high importance, it could also be argued that another objective of an Ethics Committee should be to single out the most promising studies and to prioritize them. Thereby, the committee could ensure that only scientifically and ethically sound trials are being approved and performed. There are several aspects of clinical trial design and reporting that are crucial for minimizing research waste and increasing the future value of a study. They are highlighted and discussed further on.

4.1. Are there high quality preclinical data?

In 2018, a review investigated brochures presented for the ethics review of phase 1 and 2 trials to assess the quality of preclinical data used in the analysis of probable risk/benefit ratio in human trials. It showed that the majority of those investigator brochures lacked sufficient evidence from preclinical studies (Wieschowski et al., 2018). Preclinical data are key for the appropriate design of an early clinical trial. Full and credible information from preclinical research is in many cases the only source of information about a tested drug and helps to maximize both a more favourable risk/benefit balance in clinical trials and the social benefit (Vassal et al., 2013). The trials that are designed based on a detailed review of preclinical data are more likely to be valuable, and therefore should be prioritized in bioethical assessment.

While undertaking their assessment, Ethics Committees should therefore prioritize the studies that are clearly based on a detailed review of preclinical data as potentially more valuable.

4.2. In the case of pediatric trials – are high quality data available from previous clinical trials with adults?

There is a regulatory push to include children in drug development as much as possible. For example, this is evidenced by recommendations for cancer paediatric clinical trials made by the American Food and Drug Administration (Food and Drug Administration, 2020). The adoption of Paediatric Investigation Plans by the European Medicines Agency has a similar aim – to ensure sufficient data to make informed treatment-related decisions, thus accelerating the development of paediatric therapies and reducing off-label use (European Medicines Agency, 2018). It is certainly true that such an approach leads to more therapies being available for children and adolescents, but it can be argued that there is still a need for caution. While according to the aforementioned American recommendations, paediatric participants should be enrolled in adult trials, they specify that this should be done gradually, ideally in staggered cohorts. Also, the trial design should reflect additional measures, such as long-term follow-up of paediatric patients and monitoring for age-related differences in the therapy safety profile. Another approach is to wait for relevant data from adults before initiating any paediatric trials. Adult data, together with experience from preclinical studies are another important factor helping to ensure a more favourable risk/benefit balance in paediatric trials. For instance, establishing the maximum tolerated dose – the main aim of phase 1 cancer trials – in adults first can make paediatric phase 1 trials safer and more beneficial. This means that researchers and trial designers already have crucial information, and the adult maximum tolerated dose is a solid base for establishing a first dose in a paediatric trial. Obviously, this safeguard cannot be kept in child-specific diseases or in the case of high profile drugs, such as clofarabine. It was granted accelerated approval by the American Food and Drug Administration in December of 2004. It was the first to receive approval for paediatric use before adult use and was also the first new drug to be approved for paediatric use in leukaemia in more than a decade (Pui and Jeha, 2005).

4.3. Is the study based on a strong research hypothesis?

As outlined in paragraph 2.1., phase 1 trials testing more malignancy types at the same time may have a worse risk/benefit ratio than trials testing only one type of malignancy. Regulators should be cautious about trial designs that utilize this approach. Apart from testing a narrow therapeutic scope, another feature of a potentially valuable trial would be designing the cohorts based on strong evidence from previous clinical, pre-clinical, and basic research.

The ideal approach would be to do sample size calculations, which would ensure that the researchers know how many patients and dose levels are really needed to answer their research question. This, however, is problematic for early-phase clinical trials, such as phase 1 and 2. For most phase 1 studies, sample size calculation in a traditional sense is impossible. These are generally small trials that do not test efficacy, therefore no judgements on desired effect size can be made. Traditional sample size calculations may be feasible only in some selected phase 1 studies that are already enrolling the target population (not healthy volunteers), and testing preliminary efficacy outcomes, as is common for cancer phase 1 trials. While there is consensus that the standard methods used in phase 3 trials are not appropriate for early or pilot clinical trials, there is little agreement over which methods should be used, and there

has been some discussion on how to approach this issue (Stallard, 1998, 2011). For both phase 1 and phase 2 studies, a calculation that is based on size and power, as is typical for phase 3, may not be appropriate. Studies of earlier phases are more exploratory than confirmatory in nature, thus the use of Bayesian methods, specifically decision theory models, are proposed. Stallard explains that for phase 2, rather than focusing on estimation or hypothesis testing, it is appropriate to treat them as a problem in decision analysis and use gain functions. The aim should not be on how to reach the correct conclusion with low error rates, but what is the best course of action following the phase 2 study. He also outlines that the approach may be based on different outcomes studied in phase 2, such as the number of patients successfully treated or costs and the potential financial gains connected to the drug development programme (Stallard, 1998). It is, however, important to note that phase 1 and 2 are highly varied and the method that is most appropriate for a randomized phase 2 trial, which is to be a smaller version of the phase 3 trial that will follow (same objective, method of evaluating efficacy, and primary endpoint), may not be suitable for a small phase 1 trial in healthy volunteers. Regardless of the chosen approach to test the statistical robustness of a given study, it may prove beneficial to prioritize the approval of trials that employ such methods. When a trial has some statistical consideration factored into its design, one could suppose it is based on stronger reasoning. This strong reasoning would ensure that even if its participants are still subjected to higher than minimal risk, there is a greater chance that the study will provide valuable information.

4.4. Has the trial protocol been registered?

Other sources of waste, such as publication bias, cannot be easily assessed prospectively by review bodies. Always requiring prospective registration of trials in order for them to be eligible for assessment may be a good way of avoiding future publication bias. This would make more data (both positive and negative) available for value and risk assessment, driving biomedical research forward (London and Kimmelman, 2015). Although the idea of avoiding publication bias by the prospective registration of human studies is not new, and registries have been around for some time, registering a trial before it enrols any participants is not always considered a prerequisite for its implementation or publication (Dickersin, 2003, 2012; International Committee of Medical Journal Editors, 2019). Registration in databases such as ClinicalTrials.gov or EudraCT is mandatory for applicable clinical trials using investigational medical products that are conducted in the USA or the European Union respectively, but such requirements are still not a worldwide practice (ClinicalTrials.gov, 2019; EudraCT, 2019). There are also some concerns about discrepancies between the ClinicalTrials.gov database of results (reporting of which is required for applicable clinical trials in the USA) and what is subsequently presented in a peer reviewed publication (Hartung et al., 2014).

In Europe, specific regulations require the summary of study results to be made publicly available in the EudraCT database within a year of study completion (European Parliament and Council, 2012, 2014). Unfortunately, a recent European Medicines Agency report found that approximately 32% of trials registered in the EudraCT database still lack results, and thus are not in compliance with the publication requirements (European Medicines Agency, 2019). What is interesting, commercial sponsors, such as companies, were publishing more results than non-commercial sponsors (i.e. academia, 77% vs 23% respectively). A recent cross-sectional analysis looked at interventional clinical trials registered in ClinicalTrials.gov, affiliated with at least one Polish academic medical centre (i.e. a medical university or an academic medical institution with clustered teaching hospital or hospitals), completed between 2009 and 2013.

When the academic medical centre was a "lead" facility (i.e. the trial could be considered non-commercial and Polish-based), the analysis showed that around 45% of registered trials were in compliance with the requirements – the results were posted in the database within 12 months and published as a journal article within 24 months of the primary study completion date (Strzebonska et al., 2020).

There have also been some non-government campaigns aimed at raising awareness of publication bias. The AllTrials campaign, for example, calls for all past and present clinical trials to be registered and their results reported as recommended by the Declaration of Helsinki (Pierson, 2017). Together with University of Oxford academics, AllTrials developed and launched an automated clinical trials tracker, which identifies ClinicalTrials.gov-registered studies that have not published results two years after the end of such a study. They found out that, as of November 2016, approximately 45% of trials conducted by major sponsors during the last decade still lacked results (All Trials Registered, All Results Reported, 2016). Other initiatives similar to the AllTrials campaign include the COMPare trials database, which focuses on the consistency of pre-specified and reported outcomes, and OpenTrials, which at its core is a community driven database of available clinical trials documentation ("EBM DataLab website," 2019).

Furthermore, in a recent legal dispute between PTC Therapeutics International Ltd. and the European Medicines Agency, the European General Court stated in its judgement of 5 February 2018 that clinical study reports should not be considered confidential and should be available to the public in their entirety ("Judgment of the General Court (Second Chamber), Case T-718/15 of PTC Therapeutics International Ltd," 2018). Such rulings may very well be bringing us closer to widespread public availability of essential clinical trial data. The problem of publication bias and under reporting of trials that are deemed unsatisfactory in any way may lead to disastrous outcomes, as evidenced by the TGN 1412 debacle described above (Goldacre, 2012). Prospective registration of the study protocol is also crucial for the future assessment of result quality. A 2016 systematic review of 20 paediatric trials found major discrepancies between clinical trial registry records and their published manuscripts. The trials selectively reported main outcomes (or failed to report them altogether), modified primary or secondary outcomes, contained discrepancies in sample size, failed to respect inclusion or exclusion criteria, or terminated early without justification (Rosati et al., 2016). Study sponsors often do not require study registration or reporting of results (Whitlock et al., 2019) and may even impose publication restrictions (Stretton et al., 2016). A trial that is committed to disseminating all its results from the start is more likely to provide value than the one that is not. Even though the reporting quality of the pre-specified outcomes cannot be assessed by Ethics Committees before the start of a study, pre-existing plans for sharing data (providing access to anonymous data on sharing platforms, plans for interim reporting, etc.) can be a hallmark of a valuable study. It is, of course, important to note that trial registration does not guarantee the timely dissemination of results by itself (Ross, Mulvey, Hines, Nissen, and Krumholz, 2009). It may, however, facilitate independent scrutiny by bioethicists and researchers, helping to identify red flags for future research.

4.5. If the participant population is limited – should the trial in question be given priority?

Other aspects of waste in paediatric clinical trials that should be considered in prospective committee assessment are recruitment feasibility and redundancy in research. This is especially evident in the case of paediatric oncology trials where the rarity of many

childhood cancers might make recruitment challenging. Even if paediatric phase 1 trials are carefully designed and planned, with relevant sample size calculations, they run the risk of competing with each other to recruit eligible participants from the same limited pool of patients. This competition may result in longer completion times or trials being terminated early, unable to recruit a sufficient number of participants. There is currently no centralized effort to actively manage this issue apart from the American Best Pharmaceuticals for Children Act, calling to develop an annual list of priority needs in paediatric research to help accelerate the development of the most promising drugs (Alfano et al., 2016). The review bodies would need to have access to such data to be able to prioritize the most valuable trials. In order to avoid the issue of redundancy in research that focuses on less pressing needs, they should also be able to ensure that the allocation of research resources favours conditions that are responsible for the greatest disease burden. A 2016 cross-sectional review of ClinicalTrials.gov records found that the number of paediatric trials performed in various conditions was only moderately correlated with the global disease burden (Bourgeois, Olson, Ioannidis, and Mandl, 2014).

5. Conclusion

While many failures in clinical trials are due to the poor performance of the tested treatment, they may also result from the cumulative effects of research waste. These effects may have profound consequences, both from financial and ethical standpoints. As outlined in this article, they may diminish the scientific and social value of a clinical trial – sometimes even leading to severe consequences or loss of life. There is a need to constantly evaluate clinical trials, starting from the planning stage, all the way to completion. Additional steps should be taken to minimize research waste by ensuring that studies are based on high quality data, have a strong research hypothesis and are fully committed to disseminate their results upon completion. There are several potential approaches ensuring that only the most valuable research gets approved by regulators and funded by sponsors.

Most hallmarks of research waste outlined above can be observed early. Therefore, the first of the proposed approaches may be to require more detailed evaluation from Ethics Committees or other reviewers/regulators. Broadening the scope of this assessment in such a way as to include prospective scrutiny of features of potential research waste would greatly benefit trial participants and future patients. However, doing it right would require extensive modifications to the existing system of approving new clinical research. Ethics Committees, with their current make-up and responsibilities, may be unable to provide detailed, informed, and meaningful opinions on clinical trial design, research methods and planned statistical methodology. For example in Poland, Ethics Committees currently provide assessment of the ethical issues, importance and feasibility of proposed research, but usually do not question the scientific merit of a trial beyond what is required for judging the risk/benefit ratio (Czarkowski, 2012). Apart from physicians, they include members of different professions, such as clergy, philosophers, lawyers, pharmacists and nurses. They, however, rarely include anyone else, as only these five professions are recommended in the legislature (Ministerstwo Zdrowia i Opieki Społecznej, 1999; Czarkowski and Różanowski, 2009). It would be enormously beneficial to change these recommendations to encourage the inclusion of statisticians, health technology assessment specialists or other clinical trial specialists as full-time Committee members. This would ensure that these bodies

are truly competent in prospectively evaluating potential research waste and the social value of a given study. Appointing new, specialized Committees or creating parallel expert panels in the existing ones may help decrease the workload created by the proposed, more detailed evaluation.

Modifying or dismantling the existing network of Ethics Committees in order to improve their capabilities of assessing trials for potential research waste may, however, create entirely new problems. The specialization of Committees may require them to lose one of their core strengths, i.e. experts who are or were "trial practitioners". They may not be specialized in clinical trial assessment, but have sufficient experience in the field, as required by Polish law (Ministerstwo Zdrowia i Opieki Społecznej, 1999). Therefore, the second, alternative approach would be to place more responsibility on the researchers and research sponsors themselves. Pre-registration of research protocol, providing a detailed, systematic review of relevant literature or preparing a detail analysis plan may all be pre-requisites for a Committee assessment. Attaching such documents or checklists in the dossier submitted for approval may minimally strain the Committees, but the effort by researchers in including such material may increase the quality of the proposed trials.

In Europe, the upcoming regulation on clinical trials of medicinal products for human use may be a great opportunity to implement the changes proposed above. It will repeal the existing Directive 2001/20/EC, leaving much to be decided upon at the national level, for instance, issues relating to the ethical assessment of new clinical trials. However we approach the issue of research waste in the future, activities aimed at its reduction and increasing the social value of individual clinical trials should focus on implementing solutions that promote and strengthen the culture of scientific integrity in both the local and international academic communities.

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Wpływ marnotrawstwa badawczego na rzetelność i integralność naukową badań klinicznych[3]

Pomimo postępów w medycynie i metodologii badań oraz ogromnych nakładów finansowych, wiele badań klinicznych nie dostarcza spodziewanych rezultatów i nie prowadzi do wprowadzenia na rynek nowych, skutecznych i bezpiecznych leków. Choć może to być wynikiem braku skuteczności testowanej interwencji, wiele niepowodzeń w badaniach klinicznych może być spowodowane błędami w ich planowaniu, prowadzeniu i analizie. Wraz z przypadkami nierzetelności naukowej, brakiem raportowania wyników i zjawiskiem *publication bias* składa się to na zjawisko marnotrawstwa badawczego, wywierającego negatywny wpływ na rzetelność i integralność naukową badań. Błędy te mogą narażać zdrowie uczestników badań. Niniejszy artykuł przedstawia źródła marnotrawstwa badawczego w badaniach klinicznych, ze szczególnym uwzględnieniem badań wczesnych faz, do których włącza się dzieci jako uczestników. Omawia również oznaki marnotrawstwa, które mogą zostać ocenione przez komisje bioetyczne, proponuje rozwiązania zmniejszające negatywne skutki marnotrawstwa badawczego, wzmacniając rzetelność naukową nowych badań klinicznych.

Słowa kluczowe: badania kliniczne, bioetyka, marnotrawstwo badawcze, pediatryczni uczestnicy badań, rzetelność i integralność naukowa.

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