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Corruption in vaccine research and clinical trials

Risks in low-income countries

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Clinical trials that take place in a range of countries ensures that vaccines are effective for different populations and bring opportunities for researchers and investment into a country's medical infrastructure and equipment. However, corruption risks can disrupt and dissuade vaccine research, particularly in lower income countries. To mitigate this, several integrity measures can be put into place to ensure that clinical trials are conducted safely, transparently and effectively.

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Query

What are the corruption risks associated with vaccine research and clinical trials, particularly in low-income countries? Which measures can be taken to limit these risks?

Main points

- Currently, the majority of vaccine research takes place in higher income countries, largely because the funding tends to originate in these countries. However, research in low-income countries is also increasing, which can benefit local populations through the wider distribution of more effective vaccines.
- There are corruption risks when conducting vaccine research and clinical trials, and this may be exacerbated in contexts where there is weaker regulatory oversight. These can include the risks of undue influence by large pharmaceutical companies, bribery and misappropriation of the research funds, and distortion of the data produced during the clinical trial to favour particular stakeholders' objectives. Corruption in clinical trials in low-income countries also discourages further investment and leads to the exploitation of local populations.
- These risks can be mitigated with a combination of several measures, including ensuring that the trial site adheres to international guidelines, independent oversight of the research and risk assessments. Red flags indicating evidence distortion can also trigger additional monitoring of the trial site.

Contents

Background

Vaccines reduce the risk of disease by working with the body's natural defences to build protection. Currently, it is estimated that immunisation programmes prevent around 3.5 million to 5 million deaths globally every year (WHO n.d.). Conducting vaccine research therefore ensures that the most effective treatments reach those who need them and provides critical insight for government decisions on which vaccines to distribute (Bruckner 2017). Nonetheless, there are global inequalities in access to vaccines and immunisation programmes. The recent Covid-19 pandemic in particular exposed these inequalities, with wealthier nations securing vaccines far more quickly than low-income nations.

Clinical trials form the foundation for evidence-based medicine and are the key component of vaccine research and development (Mardini et al. 2024). They are funded by public or private investment, or a mixture of both (Petkov and Cohen 2016:10). The development of vaccines involves different stages, typically over the span of several years. Preclinical trials involve studying the pathogen and antigens and then testing prototype vaccines on animals, a step which aims to eliminate vaccines that are toxic or do not induce protective immune responses (John Hopkins n.d.). After this, vaccines enter clinical trials where they are tested on human subjects of different group sizes to assess their effectiveness (John Hopkins n.d.). Each of these phases takes between one and ten years respectively, although these timelines can be accelerated under exceptional circumstances (John Hopkins n.d.). Once a vaccine has passed these phases, it enters the regulatory approval process where a responsible agency reviews the vaccine and then, if approved, manufacturing is scaled up (John Hopkins n.d.).

Low-income countries,[1] particularly those in sub-Saharan Africa, are largely underrepresented in the clinical trial stages (WHO 2024:6; Egharevba and Atkinson 2016). For example, a 2018 study found that 83% of clinical trials had been conducted in 25 high-income countries and less than 5% had been conducted in 91 lower-middle or low-income countries (Khoja et al. 2019). Although some trials do take place in low-income countries, these are generally funded by international donors or by foreign companies as opposed to funded by governments and entities in low-income countries (WHO 2024:6).

[1] This Helpdesk Answer uses the World Bank classification of economies which is based on gross national income per capita.

The WHO (2024:6) has raised concern about this disparity, noting medical research in higher income countries often prioritises their own healthcare needs, while populations in low-income countries bear the greatest burden of preventable diseases worldwide. Scientists and researchers from low-income countries have also highlighted inequalities they experience compared to colleagues from higher income countries. For example, in 2014, the Nairobi Industrial Court ruled that six Kenyan doctors in an international partnership researching malaria and other diseases had been passed over for promotion and training in favour of their European colleagues (Nordling 2015). Moreover, some researchers from low-income countries contend that, where they are included, this is inclusion is merely 'tokenistic' (Nordling 2015).

Conducting clinical trials in low-income countries is important for several reasons. They often result in upgrades and renovations to the physical infrastructure of health institutions, additional medical supplies and medical equipment for the host country (Egharevba and Atkinson 2016). Conducting research in low-income countries can foster capacity building and lead to functional international networks and a wider more equitable global health landscape and also helps to counteract the 'brain drain' (WHO 2024:7; Marincola and Kariuki 2020). Finally, in regions such as sub-Saharan Africa, there is a particularly high burden of infectious diseases (Ndwandwe et al. 2019). Evidence suggests that one country's population reacts differently to a vaccine from another,[2] making it important that clinical trials for vaccines are conducted across different populations (Ndwandwe et al. 2019).

The literature points to several reasons for the global disparity in vaccine research. One major reason is that most of the funding for clinical trials originates in higher income countries (Mumtaz et al. 2024). A second is that medical research is time-consuming and costly, with pharmaceutical companies, universities and other research groups conducting around 20,000 clinical trials involving over 2 million patients every year costing approximately US$60 billion worldwide (Bruckner 2017:3). Other frequently cited reasons are a lack of infrastructure and resource availability in low-income countries as well as fewer trained researchers (Grover et al. 2017; Ndwandwe et al. 2019).

Another obstacle to conducting clinical trials in low-income countries is corruption (Egharevba and Atkinson 2016). Corruption in the health sector can appear in many ways. It generally takes the form of bribery in the provision of medical services, procurement corruption, abuse of high-level positions and networks, undue reimbursement claims, fraud and embezzlement, and institutional corruption (European Commission 2013:5; Sommersguter-Reichmann and Reichmann 2024:3).

[2] Different populations react differently due to previous medical treatments, socioeconomic factors, and race and ethnicity, all of which impact how drugs and medicines affect groups of people (Artiga et al. 2021).

In the area of research and development more specifically, it tends to manifest as rigged research, undue influence and bribery in approvals for grants and subsidies (Merkle 2017).

Despite disparities in the location of clinical trials worldwide and concerns of corruption and unethical behaviour where these do take place, there are indications that that research in low-income countries is growing (Mardini et al. 2024). All major pharmaceutical companies now have a presence in sub-Saharan Africa, with South Africa and Nigeria being the most represented in clinical trials in the region (Ndwandwe et al. 2019). There is also a growing collaboration between different African countries in a number of trials, showing encouraging progress in the development of vaccines which are tailor-made for the African context (Ndwandwe et al. 2019).

Therefore, to ensure that vaccine research and clinical trials succeed and continue to take place in low-income countries it is important that they control the risk of corruption. This Helpdesk Answer examines some of the corruption risks associated with vaccine clinical trials that involve human subjects in low-income countries and then outlines suggestions from the literature on how to safeguard these projects against such risks. This paper primarily focuses on low-income countries, but in some of the sections it also includes observations from lower middle-income countries too, as literature and data on low-income countries is limited.

Moreover, it primarily includes studies on vaccine related research, but it also supplements this with findings drawn from other medical fields that are still applicable. Given that most funders of vaccine research and clinical trials in low-income countries are large pharmaceutical companies and international sponsors based overseas, this paper mostly examines the cross-border challenges that these projects face. While there are domestic funders for vaccine research and clinical trials, the majority is funded by overseas investors, and therefore most of the literature on the topic focuses on the risks posed by this structure.

Corruption risks

Undue influence

Undue influence refers to the ways in which interest groups such as companies, professional groups or public interest groups try to influence the decision-making process (Bosso, Martini and Ardigó 2014). Interest group influence is not a corrupt or illegitimate activity in itself, but when it is opaque and disproportionate it may lead to undue influence, corruption and even state capture when private interests substitute themselves over public good as the main driver of policy and regulation (Bosso, Martini and Ardigó 2014).

Pharmaceutical companies, who are the primary funders of vaccine research and clinical trials, can influence national political systems through lobbying, through their large spending power and by funding candidates that support their position (Kohler et al. 2016:32). For example, estimates suggest that in 2009 the industry association Pharmaceutical Research and Manufacturers of America (one of their member companies being Pfizer) spent over US$25 million on lobbying (Kohler et al. 2016:32). However, the perpetrators of undue influence in this context may not only be pharmaceutical companies but other interest groups such as research institutes or other international donors.

This influence may result in the dismantling of oversight of activities in the sector. As some experts note, while major patent-based research pharmaceutical companies commit themselves to developing products to improve health, many of the drugs that they develop are little better than existing products and even have the potential to cause adverse reactions (Light, Lexchin and Darrow 2013:591; Kohler et al. 2016:8). This is largely due to the financial incentives to bring new drugs to the market. Some (Light, Lexchin and Darrow 2013) refer to this distortion of priorities in the health sector by pharmaceutical companies as ‘institutional corruption’ that even regulators in higher income countries struggle to regulate due to the power of companies in the sector.

Clinical trials are subject to scrutiny by institutional review boards (IRBs) and federal agencies to ensure that there has been an ethical conduct of research (Mardini et al. 2024). IRBs review clinical trials to protect the rights and welfare of humans participating as subjects in research studies in universities or hospitals (HHS n.d.). However, despite these safeguards, the wider regulatory infrastructure that could detect corruption and other unethical behaviour in low-income countries is often under-funded (Lahey 2013:303). In one study, only 56% of the 670 researchers

surveyed in developing countries reported that their research had been reviewed by a local IRB or health ministry (Mardini et al. 2024).

While higher income countries struggle to regulate pharmaceutical companies, this impact can be even more greatly felt in low-income countries. Mardini (2024) notes that the strict regulations in countries like the US and potential cost savings have both been the drivers to lead research sponsored by pharmaceutical companies to move to low-income countries. This profit-driven focus coupled with weaker oversight may lead to vulnerable populations being exploited (Mardini 2024), which will be explored further in the following sections.

As an example of undue influence by the pharmaceutical sector, in 1996, Pfizer undertook an illegal trial of an unregistered drug when the company enrolled almost 100 Nigerian children with meningitis in a trial to test its antibiotic trovafloxacin (Trova) against ceftriaxone during a meningitis epidemic (Lenzer 2006). A class action suit filed on behalf of the children's families in New York alleged that Pfizer did not inform families that trovafloxacin was an experimental drug and failed to obtain informed consent.

The report later released by the Nigerian government was never made public, and Pfizer stated that it 'conducted this trial with the full knowledge of the Nigerian government and in a responsible way consistent with Nigerian law' (Lenzer 2006). Experts have questioned the study's methodology and data as well as Pfizer's failure to publish the study. While there is no explicit evidence of Pfizer's influence over the Nigerian government, the apparent complicity of state officials with this clinical trial indicates that the private company had a vast amount of influence over the outcome of the investigation.

Bribery

In most countries, clinical trial sites are hospitals that are government-owned or controlled, with doctors who are publicly employed. Therefore, overseas pharmaceutical companies and other sponsors interact with various public officials throughout the project, which brings the risk of bribery and kickbacks (Hanfin, Barnes and Berg 2016; Chen et al. 2019). Any payment generally made in connection to overseas clinical trials should be monitored rigorously by the sponsor as the healthcare professionals may be considered foreign officials under the Foreign Corrupt Practices Act (FCPA) and other anti-corruption laws (Chen et al. 2019:2). Moreover, many researchers work in healthcare institutions that are owned in whole or part by government authorities, and clinical investigational product supplies often flow through government licenced distribution agents (Chen et al. 2019:2).

The risks of bribery tend to be higher in low-income countries compared to others. The World Bank collects data on the incidence of foreign bribery, and, in 2023, it reported that 16.7% of companies stated experiencing at least one bribe payment request in low-income countries, compared to 14.1% in middle income countries and 10.9% in higher income countries (World Bank 2023).

Misappropriation of funds

Egharevba and Atkinson (2016) conducted interviews with healthcare professionals in Nigeria, Ghana, Uganda, Egypt and Liberia and pharmaceutical employees in Europe and South Africa. Their interviews with pharmaceutical professionals uncovered a concern of misappropriation of resources (such as equipment and payments) which may be given to hospital sites and researchers for clinical trials. Previous cases of aid being misappropriated in sub-Saharan Africa made shareholders hesitant about investing in research in the region (Egharevba and Atkinson 2016).

For example, one multi-year research project with a multi-million-dollar budget conducted by a US based NGO in a city in eastern Africa (details from the report are anonymised) around US$2,000 was missing after a turnover of project staff (U4 2008:3). The staff began a review of all the expenditures and withdrawals of cash from the account over the previous six months and found that a total of US$13,000 was missing, with the most likely cause being embezzlement. The project lacked controls and maintained few tracking methods, and staff were not required to sign receipts for receiving project funded resources. These oversights led to staff taking project money for their own personal use (U4 2008).

As another example, in Taiwan, professors from the country's top universities were charged with using false receipts to claim reimbursements from research funds (Leung 2013). They had fraudulently obtained reimbursements between the equivalent of US$1,700 and US$17,000 to buy personal items such as electronics, television sets and shopping vouchers (Leung 2013).

Evidence distortion and conflicts of interest

In one 2017 study, an estimated 44% of 150 clinical trials contained at least some flawed data such as flawed statistics, incorrect calculations or duplicated numbers (Van Noorden 2023). In 26%, the papers had so many problems that the trial was impossible to trust, either through the authors' incompetence or deliberate fraud (Van Noorden 2023). While these clinical trials were predominately in

anaesthesiology, there has been evidence that this is widespread throughout different medical fields (Van Noorden 2023).

Evidence distortion in research and clinical trials can include:

- spin, which is the use of specific reporting strategies to highlight that the treatment is beneficial, despite a statistically non-significant difference for the primary outcome, or to distract the reader from the statistically non-significant results (Mahtani 2016)
- misuse of statistics
- selective reporting of partial results which can include omitting data or results so that the research is not accurately represented (George and Buyse 2015)
- and data manipulation

However, not all evidence distortion is driven by corruption. It can also be driven by factors such as confirmation bias or the career ambitions of scientists (Bruckner 2017:4). Some evidence distortion, such as confirmation bias, may even be unintentional.

Gupta (2013) highlights some of the early red flags of research fraud in clinical trials that should prompt additional monitoring and scrutiny of the data. These include 100% drug compliance, identical lab on electrocardiogram results, no serious adverse events reported and subjects adhering to inspection requirements (Gupta 2013). Major differences in trends at one site from the others, unusually fast recruitment, very few withdrawals, very few adverse events being reported, all drugs being dispensed in a similar manner or repeat postponement of meetings are some additional indicators that should prompt increased monitoring of the clinical trial site (Gupta 2013).

Evidence from a narrative review of 672 papers published between 2013 and 2022 also found that the misuse of high-level positions and networks (which can include researchers providing biased evidence) is the second-most common form of corruption reported in the African and Asian regions (Sommersguter-Reichmann and Reichmann 2024:6). Because both actors involved, researchers and research organisations, have an interest in trials succeeding, this can potentially lead to a conflict of interest (Petkov and Cohen 2016:10). This can lead them to under-report the negative findings or select a study design that will show the product in the best way (Petkov and Cohen 2016:10). These risks may be particularly pertinent in low-income countries where researchers already suffer from inequalities compared to their colleagues from wealthier nations and are influenced by the goals of large pharmaceutical companies.

According to one interviewee from Egharevba and Atkinson's (2016) study, there is the perception in low-income countries that major pharmaceutical companies from

higher income countries behave poorly in the way that they publish data, withhold data and manipulate clinical studies to alter the outcomes of medicines so that they are more favourable than they would otherwise be. The interviewee noted that this evidence distortion would occur if the trials financed by large pharmaceutical companies took place in low-income countries (Egharevba and Atkinson 2016).

Other ethical concerns

Many of the drugs trialled in low-income countries have since become unavailable for patients in those same countries, raising ethical concerns of conducting such clinical trials in the first place (Egharevba and Atkinson 2016). Some call this 'exploitative' of the populations in low-income economies (Marincola and Kariuki 2020). Evidence from clinical trials in India and South Africa found that the clinical trials led to market authorisation in the EU and US without approval and distribution of the medicine in India or South Africa (Limaye et al. 2015).

Additionally, Bittker (2021) argues that communities in low-income countries that take part in clinical trials are more vulnerable due to their socioeconomic disadvantages such as the need for food or compensation and lack of access to healthcare, which can prevent them from giving consent freely. This can be aggravated by the large pharmaceutical companies that may neglect participants' welfare to increase their own profit (Bittker 2021).

There is also the issue of potential coercion of vulnerable participants in clinical trials (Egharevba and Atkinson 2016). In countries where there are issues with access to healthcare, patients are unable to give genuine consent as turning down clinical trial participation may mean that they are turning down treatment completely (Petkov and Cohen 2016:10). Additionally, even when researchers believe that consent is technically obtained in low-income countries, the potential linguistic and cultural barriers to 'clear and noncoercive communication' between investigators and patients may still raise ethical questions (Lahey 2013:304).

Egharevba and Atkinson's (2016) carried out interviews with pharmaceutical industry stakeholder members who reported being concerned about the existence of corruption during the conduct of the trial and around the perception of being corrupt or exploitative even if the research was ethical. Although some of the concerns have been legitimate, the authors note that the mutual suspicion of corruption and unethical behaviour from healthcare professionals in both higher income countries and those based in Ghana and Nigeria are potentially exaggerated, in part due to historical cases of corruption (such as the Pfizer scandal in Nigeria) that still leave an impact today (Egharevba and Atkinson 2016).

Gaidos (2013) examines the ethics of outsourcing clinical trials to low-income countries and whether this leads to the abuse of patients' rights in the name of science and corporate profits. He argues that increased competition and regulation in higher income countries has led to an increase in clinical trials in low-income countries without meeting a global standard of patient treatment (Gaidos 2013:27). For example, in India, there is a 30% time advantage in recruiting patients for a trial compared to the US, and the cost per patient is approximately half of that in the US.

In India, there have been multiple problems with patient's rights during the outsourcing of clinical trials from large pharmaceutical companies to the country. For example, many of the patients have been poor and illiterate or are Dalits who are considered at the bottom of the Hindu caste system (Gaidos 2013:30). Sometimes they have not been asked to sign a consent form or not even informed that they were entering a clinical trial. There were also several patient deaths after they were discharged from hospital as the families were not informed of the previous involvement in the trial (Gaidos 2013:30).

As a further example, a parliamentary panel criticised the Indian Council of Medical Research and the international non-profit Program for Appropriate Technology in Health (PATH) for their human papillomavirus (HPV) vaccine project in India (Mudur 2013). The project had administered the HPV vaccine to around 20,000 girls aged 10 to 14 years between 2009 and 2010 and had breached medical ethics and violated Indian regulations on clinical trials (Mudur 2013). There were irregularities in the informed consent papers and adverse effects were reported among the vaccinated girls (Mudur 2013). The parliamentary panel said that the Indian Council of Medical Research had 'completely failed' to perform its role as the country's agency for overseeing medical research and had acted with 'over-enthusiasm' to work with PATH (Mudur 2013).

Finally, in 2021, it was also reported that there were ethical violations during a clinical trial of a Covid-19 vaccine that was jointly developed by India's Bharat Biotech and the Indian Council of Medical Research (India Correspondent BMJ 2021). Seven participants in the trial were not informed that they would receive either a vaccine or a placebo, and instead told that they would receive a coronavirus vaccine that would protect them (India Correspondent BMJ 2021). This was considered a 'breach of the tenant of voluntary participation without inducement or coercion' (India Correspondent BMJ 2021). The participants in the trial were also considered highly vulnerable due to their low economic status. Doctors and health rights advocates asked the trial to be halted, exclude any data from the site during trial analysis and take action against those responsible for violations.

Integrity measures

Ethical principles

There are several internationally recognised principles and guidelines for ethical clinical trials that have been developed by international bodies to help protect the safety and rights of patients and ensure data integrity in trials.

The Declaration of Helsinki was developed by the World Medical Association (WMA) as a statement of ethical principles for medical research involving human participants (WMA 2024). It recommends protecting vulnerable groups by stating that 'researchers should only include those in situations of particular vulnerability when the research cannot be carried out in a less vulnerable group or community, or when excluding them would perpetuate or exacerbate their disparities' (WMA 2024). It also notes that researchers must consider the legal and regulatory standards for research in the countries where it is performed, as well as the international norms and standards (WMA 2024).

The declaration also underscores the importance of research ethics committees and their responsibility in monitoring the trials and that these must be 'transparent in [their] functioning and must have independence and authority to resist undue influence from the researcher, the sponsor, or others' (WMA 2024). While the Declaration of Helsinki is not legally binding, it is considered best practice by medical researchers and organisations worldwide and has been used as a basis for the creation of national regulatory regimes (Gaidos 2013:28).

The Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the WHO has also produced International Ethical Guidelines for Health-related Research Involving Humans. Guideline 2 refers to research in low-resource settings, which obliges sponsors and researchers to make every effort to make available as soon as possible any intervention or product developed for the population and community in which the research was carried out, ensuring fair distribution of benefits of medical research (CIOMS and WHO 2016:3). It also recommends consulting and engaging with communities in making plans for any intervention or product developed (CIOMS and WHO 2016:3).

To prevent conflicts of interest during trials, it states that research institutions, researchers and research ethics committees should develop and implement policies to mitigate conflicts of interest, as well as ensure that disclosures of interests are submitted to research ethics committees and that studies are evaluated in light of these disclosures of interests (CIOMS and WHO 2016:94).

The ICH Guideline on general considerations for clinical studies describes the internationally accepted principles and practices in the design and conduct of clinical studies. This includes the protection of clinical study participants (page 5), methods to reduce bias in the results of the trials (page 17), best practice for statistical analysis (page 18) and safety monitoring (page 21), among others (EMA 2021).

A final resource is the WHO's guidance for best practices for clinical resources, which is a useful guide on how to ensure that medical research and clinical trials are effective and conducted appropriately. It notes that good trial monitoring and auditing is also important (WHO 2024:26). A trial steering committee responsible for the governance of the trial is recommended by the WHO (2024:25). This should maintain the scientific and ethical integrity of a trial and provide advice on the appropriate course of action. Membership of trial governance structures should reflect the necessary expertise to scrutinise key roles, responsibilities and risks, and should be independent from trial sponsorship (WHO 2024:25).

Regulatory oversight and agencies

The World Health Organization (WHO) developed the global benchmarking tool for evaluation of national regulatory systems of medicines and vaccines, which is designed to assess and improve the regulatory capacities of national health authorities that oversee vaccine and medicine development. It enables the WHO and regulatory authorities to identify areas of strength and areas of improvement, and section 08 (page 273) focuses specifically on clinical trial oversight. The WHO also provides standards for vaccine quality, safety and efficacy standards (WHO n.d.).

The WHO benchmarking tool includes indicators such as requirements for monitoring and reporting of adverse events during clinical trials (page 283), a defined structure with clear responsibilities with oversight activities in a clinical trial (page 287), sufficiently competent staff to perform clinical trial oversight activities, and advisory committees to review clinical trial applications, post-approval safety and compliance issues (page 295), among others. However, the implementation of the benchmarking tool is a lengthy process, taking between two and five years (Mardini 2024).

National regulatory agencies are responsible for reviewing vaccine data for their quality and safety as well as ultimate approval for the population's use. Gupta (2013) refers to both the Office for Human Research Protections (OHRP) in the US and the Research Council of Finland as best practice examples of public agencies that produce guidelines on human research subject protection and research integrity during trials. The OHRP provides leadership in the rights, welfare and well-being of human subjects in research conducted or supported by the US Department of Health and

Human Service (OHRP n.d.). It also exercises regulatory oversight and responds to reported incidents in research (OHRP n.d.). The Research Council of Finland is a government agency that funds high-quality research and provides expertise to Finnish and collaborative networks (Research Council of Finland n.d.).

Development agencies also play a key role in encouraging the strengthening of national regulatory frameworks, particularly when funding vaccine research overseas in low-income countries. Hussmann (2020) provides recommendations directed towards donors to help prevent and detect corruption in the health sector. One of these includes strengthening the transparency and accountability of key policy-making and regulatory processes, including those that manage research and medical trials (Hussmann 2020:51). Donors can also provide systematic technical and political support to strengthen health sector regulatory and oversight institutions to help create mechanisms for transparency and integrity (Hussmann 2020:51).

Finally, it is important that professional and academic institutions apply appropriate sanctions against researchers found guilty of unethical behaviour or corruption (Kohler et al. 2016:35).

Nonetheless, Kohler et al. (2016:30) argue that, despite the efforts of international organisations such as UNDP and the World Bank focusing on strengthening countries' legislative and regulatory frameworks by assisting the development of new laws and institutions, these efforts have been insufficient. Countries with weaker levels of governance have still been limited by their inability to effectively ensure that government institutions carry out existing and new laws, particularly when faced with large international pharmaceutical companies.

Trial site selection

Once a potential site for a trial has been identified, a pre-study site visit should take place (Silva 2018). This is to assess how suitable the site is for the trial and to verify that the investigator has the personnel, time, subject population and facilities and equipment to conduct the study (Silva 2018; Hanifin, Barnes and Berg 2016). It is important at this point that all the information regarding the site is gathered, reviewed, and evaluated objectively to ensure that the site selection is made in a transparent manner (Silva 2018).

Sites should also be able to demonstrate compliance with international guidelines such as the ICH guidelines and the ethical guidelines on clinical trials involving human subjects. This is an important step in the due diligence process and to ensure a site is selected where ethical concerns and corruption risks will be less likely. Ethical reviews should also consider whether there are sufficient resources available

at the trial site to avoid any impact on routine patient care (WHO 2024:50). Once the site is selected, it should be reviewed by the ethics committee to examine compliance with regulatory standards and the quality of data (where applicable) deriving from previous trials that have taken place on the site.

Miller and Millium (2022) discuss the ethical considerations that should be made in international clinical trial site selection. They argue that the ethical principles of social value and fair subject selection provide the appropriate guidance to support clinical trial sites in low-income counties. Social value includes whether the research will contribute to knowledge that promotes human health or not. Fair subject selection means that investigators should be inclusive in their selection of trial participants, ensuring that it is not only higher income countries that are included in site selection. This would help to ensure health equity through data provided by different populations and ensure that the most beneficial interventions reach the public (Miller and Millium 2022:3).

Many clinical trial sites are in large national centres in hospitals. However, the WHO (2024:35) also recommends extending trial sites to smaller local centres or even patients' homes (such as in decentralised trials) to facilitate larger sample sizes and to increase participation. An automated and digital process can help speed up such initiatives and increase efficiency and transparency (WHO 2024:35).

The locations of trial sites should also be made transparent, although studies have shown that currently only 37% of trials supporting FDA drug approvals have publicly available trial site locations in the medical literature or on a registry (Miller and Millium 2022:2). Another round of due diligence should be conducted once the site selection is complete to ensure that the fees paid to study sites represent fair market value (Hanifin, Barnes and Berg 2016). All payments made to the site should be traceable and monitoring of the trial sites should be regularly made to ensure that they are performing the services that they have been contracted for (Hanifin, Barnes and Berg 2016).

Risk management frameworks

An important step to before starting the clinical trial is to complete a risk management exercise to ascertain the particular corruption and other risks that may take place and how to mitigate these before they occur. This is particularly important given that foreign pharmaceutical companies and donors often conduct clinical trials overseas and work with public officials. Johnsøn (2015) sets out the basics of corruption risk management and how to integrate this into project cycles. This includes steps to:

- identify corruption risks, determine the tolerable level of risk (threshold)
- assess the level of risk (probability vs impact)
- compare actual level of risks with the tolerable threshold, decide if mitigation is required
- if mitigation is required, select the best tool based on cost-effectiveness (Johnsøn 2015:7)

Given the importance of data quality and patient safety in clinical trials, there is likely to be very low (if any) appetite for risk. Risk assessments are particularly pertinent if the sponsors of the project are overseas as they may require local knowledge to identify risks.

Oversight during the clinical trial

There are several additional steps that can be taken to ensure integrity at the clinical trial site throughout the project. Gupta (2013) examines fraud and misconduct in clinical research and suggests that firstly strengthening institutional review boards (IRBs) and ethics committees (ECs) helps to safeguard the interests of research participants. To do so, they should have internal control and review mechanisms for monitoring the ethical and quality aspects of studies. Existing regulations should also be simplified and made more effective, and all organisations generally involved in clinical research should have clear operational policies and procedures for dealing with research misconduct and fraud (Gupta 2013).

Investigator selection for clinical trials should also be based on merit and ability to perform protocol-required services, and procedures should be implemented to track the use of individual investigators over time (Hanifin, Barnes and Berg 2016). Payments should be made to investigators' institutions rather than directly to the investigator to reduce the scope for improper payment (Hanifin, Barnes and Berg 2016).

Another important component is ensuring that there is fully informed consent from patients to ensure patients are not taken advantage of. Variations of consent should be considered as, although consent conventionally takes the form of a decision by the participant, other cultures may also require a tribal chief's consent or wider community consent too (Mardini 2024). For example, a team of clinical researchers working within the Medical Research Council Unit of the Gambia discussed the challenges they faced and the strategies they developed to improve the collection and reporting of adverse events in low-income settings (Bruce et al. 2024). They noted that there were sociocultural limitations to the studies, which included low literacy rates when gaining consent and understanding of the trial. To mitigate this, they

recommend using home visits with paper or electronic forms. They also suggest that, prior to the trials, researchers should hold community engagement meetings before the start of each study to inform community stakeholders about the study and answer any questions (Bruce et al. 2024).

Whistleblower channels and community complaints mechanisms

Reports of more serious breaches in clinical trials are usually reported through government provided channels. For example, the UK government encourages whistleblowers to report to the Medicines and Healthcare products Regulatory Agency. However, it is also important that channels are set up internally within the trial site to ensure encourage reporting any incidences of misconduct or corruption.

Community complaints mechanisms provide the public with channels to report any incidence or suspicion of corruption or other malpractice and for subsequent corrective action to be taken (Transparency International 2016). A properly functioning corruption complaint mechanism has the potential to strengthen the organisation's credibility and reputation with society members, which is important when conducting clinical trials with communities, particularly those in low-income countries.

Transparency International (2016: 5-9) provides some guidance on the features of an effective community complaints mechanism:

- a wide range of reporting channels, including email, online and offline reporting tools, helplines, personal conversations, etc. These should all be free of charge, easily accessible, have the option of anonymity and be auditable
- the complaints handling procedure should be published and take into consideration any cultural characteristics or accessibility needs of the location
- all complaints should be recorded with an identifier, date and first actions for response, and two staff should conduct independent reviews of the complaints about decision-making
- complaints should be fact-checked, and this review should be independent, objective and impartial
- complaints should be recorded (such as through a database) and compliance monitoring of the complaint should be conducted
- there should be clear roles for strategic oversight of the mechanism and codes of conduct for all staff involved

Reporting by staff, whether they are the researchers or other medical staff is also important to uncovering corruption, fraud and misconduct during clinical trials. According to Terracol (2022), key components of an internal whistleblowing system include the following:

- protection of all whistleblowers or reporting persons
- an impartial person or department responsible for the operation of the internal whistleblower system
- accessible information about the whistleblowing system that is highly visible and accessible
- multiple reporting channels
- timely follow-ups to any reports

Transparency

Once clinical trial data is generated several measures can be implemented to minimise the risk of evidence distortion once the data from the trial has been collected. Bruckner (2017:7) identifies these 'five pillars of clinical trial transparency'. The first is trial registration, which involves a regulated online trial registry that is universally recognised irrespective of national requirements. This should be open to all research funders to avoid duplication of research. In many jurisdictions this is already a legal or regulatory requirement, but compliance is lacking in many places (Bruckner 2017:7).

Currently there are 17 registries approved by the WHO, which are managed by non-commercial entities and are open to the public, with the largest being Clinicaltrials.gov (US), EudraCT (EU) and the Japan Primary Registries Network (Bruckner 2017:9). Additionally, the EU Clinical Trials Regulation mandates that there be a single submission for authorisation of a clinical trial into an EU portal (the Clinical Trials Information System) and also mandates important requirements such as the protection of subjects and informed consent (EU 2022). If clinical trials are conducted outside of the EU, then they must still follow similar principles to the provisions of the regulation regarding the rights and safety of patients and the reliability and robustness of data generation (EU 2022).

The second pillar of transparency is summary results posting. This includes the obligation for researchers to post summary results onto the registry where it was originally registered to provide a publicly accessible snapshot of the headline results of a trial (Bruckner 2017:8). This enables researchers to share new discoveries without having to wait until academic publication and reduces the potential for bias and evidence distortion in the reporting of the results.

Thirdly, the publication of full trial reports mean that clinical study reports (CSRs) should also be published, which are lengthy documents that allow experts to determine how significant and reliable a trial's findings are (Bruckner 2017:8). The fourth, academic publication, is the primary communication platform for scientists and ensures that the trial results are read and shared widely (Bruckner 2017). However, currently, many results of trials are not published in journals.

The final pillar of transparency is individual participant data sharing. This involves sharing the trial related data collected on each individual participant throughout the clinical trial (Bruckner 2017). This aims to help improve understanding of the safety and effectiveness of drugs and reduces the scope for fraud (Bruckner 2017).

Alternative approaches to transparency are important during the clinical trial process. Franzen et al. (2024) developed clinical trial report cards that combine tailored feedback and guidance to investigators across several transparency practices, including prospective registration, availability of summary results and open access publication. Each card asks investigators to detail the extent to which their trial was transparent and to reflect on how to increase the trial's transparency. They also developed an info sheet with an overview of guidelines and laws relating to clinical trial transparency. Franzen et al. (2024) tested these report cards at Berlin's university medical centre, Charité Universitätsmedizin Berlin, in 155 clinical trials, and found that they were considered effective at building awareness of the transparency of the trial by the researchers and medical staff.

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