Guidance for Good Randomized Clinical Trials

May 2022

Developed by the Good Clinical Trials Collaborative

goodtrials.org

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Introduction

The role of randomized controlled trials in improving health

Randomized controlled trials (RCTs) play a central role in generating the evidence needed to inform the development and implementation of health interventions.

Most interventions have modest effects on health and disease, even if they have a large effect on intermediate features (e.g. physiological or laboratory tests). However, even modest improvements in health can be important provided any benefits are not substantially offset by detrimental effects. To establish reliably whether a health intervention has any effect requires that any biases or random errors inherent in the study design are both small with respect to the expected treatment effect.

Unfortunately, useful evidence from good RCTs is often lacking. This can be because RCTs were never done, or those that were done failed to produce scientifically robust and clinically relevant answers, or the results were never published. This can result in failure to identify and use effective interventions or the continuing use of ineffective or hazardous interventions. Such problems waste resources, cause unnecessary harm or suffering, and reduce trust in those who develop or use health interventions. It must be made easier to do good RCTs to inform the development of better interventions and the delivery of future care.

Guidance development

There is a clear need for guidance to promote the unique benefits of RCTs across all contexts and which focuses on the unique strengths of randomization while setting out the underpinning principles necessary to generate reliable results safely and ethically, regardless of context. The Good Clinical Trials Collaborative (GCTC) was established to develop and promote the adoption of new guidance to address this issue. The GCTC has brought together a wide range of individuals and organizations with an interest and role to play in the design, delivery, analysis and reporting of RCTs, and in implementing the results. This includes those who fund, regulate, design, deliver, or are responsible for RCTs, those who provide quality assurance, audit or inspection functions, research organizations, ethicists, clinicians, participants, and lay health advocates. It also includes those from a wide variety of sectors (industry, academia, government, charitable, non-governmental organizations, participant and public groups) and settings (including higher and lower income countries around the world).

Objective

The objective of this guidance is to establish the key principles of RCTs: what makes a RCT good in its design and analysis, as well as ethical and social value; and why this is so. This guidance aims to enable those involved in RCTs (in any capacity) to work out for themselves how a RCT should be designed and delivered in a particular setting.

This new guidance has been developed to be:

- **Based on key scientific and ethical principles** and focused on issues that materially matter to the well-being of trial participants and the reliability of RCT results;
- **Clear, concise, consistent and proportionate** to the context and setting in which RCTs are conducted, recognizing that there are risks associated with both usual clinical practice and a lack of reliable evidence on the effects of an intervention;
- **Forward looking, fostering innovation in health interventions and trial methods**, including the appropriate use of routine healthcare data, technologies, and designs; and
- **Flexible, widely applicable, utilizable and durable** across disease areas, intervention types, development phases, trial designs, geographies and time.

Scope

This guidance is **intended to support all individuals and organizations involved** in the planning, conduct, analysis, oversight, interpretation and funding of **all trials in which randomization is used to assess the effects of any health intervention for any purpose in any setting**. The remit includes, for example:

- **Any design**: including comparisons of two or more interventions (one of which may be to provide no additional active intervention beyond usual practice); blinded or not; parallel, cluster, crossover or other design.
- **Any health intervention:** including pharmaceutical and biological therapies; medical devices; surgical procedures; vaccines; nutritional measures; cognitive, behavioural and psychological interventions; digital and public health approaches.
- **Any purpose:** intended to support reliable evaluation of the safety and efficacy of new and existing interventions; regulatory submissions; health technology assessments; and public health strategies.
- **Any setting:** including any geographic, economic or societal context; any context including RCTs based in hospital, primary care or community settings; or delivered direct to participant.
- **Any role:** including researchers and clinicians; patient and public groups (including trial participants); regulators and other government bodies; ethics committees and institutional review boards; funders; trial sponsors (e.g. academic, commercial); the health intervention industry and those who regulate or provide audit and quality assurance functions.

How to use this guidance

This document provides the **underpinning principles** of good RCTs. The word ‘should’ implies that something is generally the right approach or a good idea but absolutes are rare. The details of how the principles are applied to any particular trial will vary and the guidelines are not intended to be applied rigidly or uncritically.

Principles of Good Randomized Controlled Trials

In this guidance, 'good' should be taken to mean reliably informative, ethical and efficient. The following principles, taken together, capture the necessary qualities of a well-planned, well-run and clinically relevant trial. The methods and approaches needed to achieve these qualities will differ in small or large ways from trial to trial but their validity is universal.

1. Good RCTs are designed to produce scientifically sound answers to relevant questions

RCTs should help resolve important uncertainties about the effects of health interventions. Depending on the context, the results may be needed to determine whether to proceed with development further evaluation of the intervention or inform regulatory licensing, clinical guidelines, and/or health policy. In each case, any uncertainties applying to the specific question(s) that remain at the end of the RCT should be sufficiently small to allow meaningful decisions to be made.

This requires the combination of:

- **Randomization without foreknowledge of intervention allocation**: so that any differences in health outcomes between the groups are either due to the effect of the study intervention or to the play of chance;
- **Adequate sample size**: to reduce the impact of *random errors* (i.e., the play of chance) on the results;
- **Unbiased assessment of outcomes**: i.e. not influenced by knowledge of intervention allocation; and
- **Intention-to-treat analyses:** to compare outcomes according to the intervention to arm to which participants were allocated and **without emphasis on data-derived subgroups**.

Good RCTs should include the following features:

Appropriate trial population

Key Message: The eligibility criteria should be tailored to the question the RCT sets out to answer. Inclusion criteria should not be unnecessarily restrictive. Efforts should be made to include a broad and varied population (e.g. with appropriate sex, age, ethnic and socioeconomic diversity), unless there is a good medical or scientific justification for doing otherwise.

Exclusion criteria should be focused on identifying individuals for whom participation would place them at undue risk by comparison with any potential benefits (e.g. based on their medical history or concomitant medication) or for whom the benefits have already been reliably demonstrated.

Why this is important: Inclusive eligibility criteria increase the relevance of the findings. They may sometimes allow assessment of whether there is good evidence of material differences in the effects (beneficial or adverse) and/or acceptability of an intervention or its delivery in any particular subgroup (e.g. based on specific genetic, demographic, or health characteristics), although statistical power to detect such differences exist may be limited.

Robust intervention allocation

Key Message: Randomization requires generation of an unpredictable allocation schedule with concealment of which intervention will be allocated to a particular participant until after the point of randomization. It should be impossible to predict in advance which individual trial participant or

individual cluster (e.g. hospital or city in a cluster RCT) the study intervention is likely to be allocated to, so that investigators, health care providers and other staff involved, and potential participants are not aware of the intervention to which they will be assigned.

Why this is important: Randomization allows for like with like comparisons so that subsequent differences in health outcomes between the groups (beneficial or adverse) are due either to the play of chance or are due causally to differences in the study intervention. Measures such as minimization may be used to reduce the size of random differences between intervention groups, provided that they are implemented in such a way that avoids potential participants and those enrolling them being able to predict which intervention will be allocated at the point of randomization. The absence of adequate allocation concealment prior to randomization can lead to selection bias (i.e. the decision to enter a particular participant in a trial can be influenced by knowledge of which intervention they are likely to be assigned to).

Adequate size

Key Message: A RCT should be sufficiently large and statistically powered to provide a robust answer to the question it sets out to address.

Why this is important: For the effects of health interventions to be reliably detected or reliably refuted then, in addition to randomization (to minimise biases), random errors must be small by comparison with the anticipated size of the effect of the intervention. The best way to minimize the impact of random errors is to study sufficiently large numbers (noting that RCTs assessing impact on discrete health outcomes such as mortality will require more participants than those assessing impact on continuous measures such as laboratory results as is often the case in early phase trials).

There are some scenarios for which it is inappropriate or challenging to randomize sufficiently large numbers of participants, such as trials assessing interventions in rare diseases. For such trials, it may be helpful to contribute to a broader collaboration to conduct the RCT or select a clinically relevant outcome for which the effect size is expected to be larger (e.g. a physiological or imaging biomarker). It may be possible to reduce the impact of random errors through the statistical analyses that are done (e.g., analyses of a continuous outcome adjusted for baseline values of that outcome would typically increase statistical power compared with an analysis of either mean follow-up levels or an analysis of mean changes in levels) or by making assessments at a time when the effects of the intervention are anticipated to be greatest.

Blinding and masking of allocated trial intervention

Key Message: Knowledge of the allocated trial intervention may influence the behaviour of participants, those who care for them, or those assessing study outcomes (particularly if these are subjective in nature). This can be avoided through use of placebo medications or dummy interventions or by ensuring that those individuals or systems responsible for assessing participant outcomes are unaware of the allocated intervention.

Why this is important: In some RCTs, knowledge of the allocated intervention can influence the nature and intensity of clinical management, the reporting of symptoms, or the assessment of functional status or clinical outcomes. This is particularly important for trials in which blinding of the allocated intervention is not feasible or desirable. Masking (or blinding) participants, investigators, health care providers, or those assessing outcomes to the assigned intervention can help prevent such issues as can the use of information that is recorded separately from the clinical trial (e.g. routine clinical databases and disease registries). These considerations are important for both the

assessment of both the efficacy and the safety of the intervention, including processes relating to adjudication of outcomes and considerations of whether an individual health event is believed to have been caused by the intervention.

Adherence to allocated trial intervention

Key Message: Efforts should be made to facilitate and encourage adherence to the allocated intervention(s).

Why this is important: If trial participants allocated to active intervention do not receive it as planned, or if those allocated to the control group (e.g. placebo or usual care) start to receive the active intervention, then the contrast between the two study groups is less. Consequently, the ability to assess any differences (beneficial or harmful) between interventions is reduced (and it is more likely to falsely conclude that there is no meaningful difference between the interventions when in fact there is one).

Completeness of follow-up

Key Message: Participant outcomes should be ascertained for the full duration of the RCT, regardless of whether a trial participant continues to receive the allocated intervention or ceases to do so (e.g. because of perceived or real adverse effects of the intervention). In some cases, it may also be appropriate to continue follow-up for many years beyond reporting the main analyses.

Why this is important: Continued follow-up of all randomized participants (even if some stop taking their assigned intervention) maintains the like-with-like comparison produced by the randomization process. Premature cessation of follow-up or post-randomization exclusion of participants should therefore be avoided since it may introduce systematic bias, particularly as the type of people excluded from one intervention group may differ from those excluded from another. Incomplete follow-up may reduce the statistical power of a RCT (i.e. the ability to distinguish any differences between the interventions) and underestimate the true effects (benefits or hazards) of the intervention. Extended follow-up can allow for detection of beneficial or harmful effects of the study intervention that may persist or emerge months or years after the initial randomized comparison.

Relevant measures of outcomes

Key Message: The outcomes that are assessed in a RCT need to be relevant to the question being addressed. These may include physiological measures, symptom scores, participant-reported outcomes, functional status, clinical events, or healthcare utilization. The way in which these are assessed should be sufficiently robust and interpretable (e.g. used in previous trials or validated in a relevant context).

Why this is important: The ways by which the consequences of the randomized intervention are measured should be sensitive to the anticipated effects of the intervention and appropriate to the study question, and in general should be applicable and meaningful for the relevant population. The choice of outcomes may vary depending on the extent of prior knowledge of the effects of the intervention (e.g. early trials may assess the effects on imaging and laboratory markers and later trials the effects on clinical outcomes). It is rarely possible or desirable to assess the full range of potential outcomes in a single RCT. Instead, there should be a focus on providing a robust answer to the specific, well-formulated question.

Proportionate, efficient and reliable capture of data

Key Message: Data collection should focus on those aspects needed to assess and interpret the trial results as specified in the protocol and should not be excessive. The extent to which information (e.g. on participant characteristics, concomitant treatments, clinical events, and laboratory markers) is detected and recorded, and the means and level of detail to which this is done should be tailored to each RCT. This should take into account what is needed to answer the trial question, the level of existing knowledge about the background health condition and the intervention being studied. The choice of data collection approach may also be influenced by considerations such as suitability, availability, and usability as well as the extent to which such information is sufficiently accurate, comprehensive, detailed, and timely.

Tools and methods for data collection, storage, exchange, and access should enable the RCT to be conducted as designed, support privacy and security, and enable reliable and consistent analyses. Digital technology and routine healthcare data can provide alternative or complementary means to record information about participants and their health at study entry, during the initial intervention and follow-up period, and for many years beyond, where appropriate.

Why this is important: The volume, nature, and level of detail of data collection should be balanced against its potential value. Disproportionate data collection wastes time and resource. It places unnecessary burden on trial participants and staff, distracts attention from those aspects of the trial that have greatest consequence for the participants, and reduces the scale (number of participants, duration of follow-up) of what is achievable with available resources. In some trials, it may be appropriate to measure some features (e.g. intermediary biomarkers) in a subset of participants, chosen on the basis of baseline characteristics or random selection, or at a limited number of timepoints. The choice of method used for data collection can have an important bearing on trial reliability and feasibility. Use of data standards can help ensure data quality and data integrity. Use of digital technology and routine healthcare data can improve the relevance and completeness of information collected (e.g. reducing loss to follow-up).

Ascertainment of outcomes

Key Message: Processes for ascertaining study outcomes should be the same in all randomized groups. This includes the frequency and intensity of assessments. Particular care should be taken to ensure that the people assessing, clarifying, and adjudicating study outcomes are not influenced by knowledge of the allocated intervention (i.e. blinded or masked outcome assessment). Equally, the methods for acquiring, processing, and combining sources of information (e.g. to define participant characteristics or clinical outcomes) should be designed and operated without access to the intervention allocation for individual participants or knowledge of the unblinded trial results.

Why this is important: If the methods used to assess, clarify or classify outcomes differ between the assigned interventions, the results may be biased in one direction or other leading to inappropriate conclusions about the true effect of the intervention. Therefore, the approach used to assess what happens to participants should be the same regardless of the assigned intervention. Those making judgements about the occurrence or nature of these outcomes should also be unaware of the assigned intervention (or features, such as symptoms or laboratory assays, that would make it easier to guess the assignment) for each participant.

Statistical analysis

Key Message: Trial results should be analysed in accordance with the protocol and statistical analysis plan, which should be developed prior to knowledge of the study results. Any post-hoc analyses should be clearly identified as such. The main analyses should follow the intention-to-treat principle, meaning that outcomes should be compared according to the intervention arm to which the participants were originally allocated at randomization, regardless of whether some of those participants subsequently received some or none of the intended intervention, and regardless of the extent to which the post randomization follow-up procedures were completed.

Subgroup analyses should be interpreted cautiously, especially if they are multiple in number, whether pre-specified or not. In general, any prognostic features that are to be used in analyses of intervention effects in RCTs should be irreversibly recorded (or sample collected) before randomization.

Why this is important: The strength of a RCT is that there is a randomized control group with which to compare the incidence of all health events. Consequently, it is possible to distinguish those events that are causally impacted by allocation to the intervention versus those that are part of the background health of the participants. Analyzing all participants according to the intervention to which they were originally allocated ('intention-to-treat' analysis) is important because even in a properly randomized trial, bias can be inadvertently introduced by the post-randomization removal of certain individuals from analyses (such as those who are found later not to meet the eligibility criteria, who are non-adherent with their allocated study treatment or who commence active intervention having been allocated to a control group).

Additional analyses can also be reported, for example, in describing the frequency of a specific side effect. It may be justifiable to record its incidence only among those who received the active intervention, because randomized comparisons may not be needed to assess large effects. However, in assessing moderate effects of the treatment, 'on-treatment' or 'per protocol' analyses can be misleading, and 'intention-to-treat' analyses are generally more trustworthy to assess whether there is any real difference between the allocated trial interventions in their effects.

One of the most important sources of bias in the analysis is undue concentration on just part of the evidence (e.g. selective emphasis of the result in one subgroup of many or in a subgroup that is defined after consideration of the data). Apparent differences between the therapeutic effects in different subgroups of study participants can often be produced solely by the play of chance. Subgroups therefore need to be relevant, pre-specified, and limited in number. Analysis of results in sub-groups determined by characteristics observed post-randomization should be avoided because if the recorded value of some feature is (or could be) affected by the trial intervention, then comparisons within subgroups that are defined by that factor might be biased. It is important to interpret results in specific subgroups (e.g. men vs. women) cautiously and consider whether they are consistent with the overall result or not. Failure to do so can lead to people in those being treated inappropriately (given an intervention that is ineffective or harmful) or untreated inappropriately (not being given an intervention that would benefit them) when there is no good evidence that the effect varies between them.

Assessing beneficial and harmful effects of the intervention

Key Message: Data generated during the course of conducting a RCT may reveal new information about the effects of the intervention which is sufficiently clear to alter the way the trial is conducted

and participants are cared for, or is sufficiently compelling to change the use of the intervention both within and outside the trial. Potential harms of the intervention should be considered alongside potential benefits and in the wider clinical and health context.

Why this is important: Not every health event that happens in a trial is caused by one of the interventions; individuals involved in a trial may suffer health events that have nothing to do with the trial or the interventions being studied. (The less healthy the participants in the RCT, the more likely that any health event is related to factors other than the intervention.)

Assessing whether signals (e.g. rates of clinical events or laboratory abnormalities) seen among those allocated to receive a health intervention are significantly more or less frequent than in the control group provides a reliable assessment of the impact of the intervention. It provides a fair assessment of which event are causally impacted by allocation to the intervention versus those that are part of the background health of the participants. In an ongoing RCT, such unblinded comparisons should be conducted by a group (such as a Data Monitoring Committee) that is independent (or firewalled) from the trial team to avoid prematurely unblinding the emerging results to those involved in running the trial.

By contrast, reports of individual events that are believed (e.g. by the participant or a doctor) to be caused by the intervention are much less informative due to the lack of a comparison with the incidence of the event in control group and the inherently imprecise judgement of causality. The exceptions are events that are rare in the types of people involved in the trial but known to be potentially strongly associated with particular interventions (e.g. anaphylaxis or bone marrow failure in association with drugs).

Harmful and beneficial effects of health interventions may have different impact or frequency, may have different time courses, and may occur in particular groups of individuals. Some interventions (e.g. surgery, chemotherapy) may be associated with little or even hazardous effect in the short-term but provide longer-term benefit. It should also be recognised that for many interventions, the benefits may not be apparent on an individual basis, such as where a detrimental outcome has been prevented (e.g. a stroke or infection).

Monitoring emerging information on benefits and harms

Key message: An independent Data Monitoring Committee (DMC) provides a robust means to evaluate safety and efficacy data from an ongoing RCT, including unblinded comparisons of frequency of particular events, without prematurely unblinding any others involved in the design, conduct, or governance of the trial. For many RCTs, particularly in earlier phase trials, the functions of a DMC could be provided internally but those involved should nonetheless be adequately firewalled from the trial team to ensure that awareness of results does not introduce bias (or the perception of bias). Some trials may not require a DMC (e.g. if the trial is short-term and would not be modified regardless of interim data).

Why this is important: All those involved in the design, conduct and oversight of an ongoing RCT should remain unaware of the interim results until after the study conclusion so as not to introduce bias into the results (e.g. by stopping the trial early when the results happen by chance to look favourable or adverse). The requirement for, and timing and nature of, any interim analyses should be carefully considered so as not to risk premature decision-making based on limited data.

A DMC should include members with relevant skills to understand and interpret the emerging safety and efficacy data. A DMC should review analyses of the emerging data, unblinded to the randomized intervention group. The DMC should advise the RCT organisers when there is clear

evidence to suggest a change in the protocol or procedures, including cessation of one or more aspects of the trial. Such changes may be due to evidence of benefit, harm or futility (where continuing the trial is unlikely to provide any meaningful new information). In making such recommendations, a DMC should take account of both the unblinded analyses of the RCT and information available from other sources (including publications from other trials).

2. Good RCTs respect the rights and well-being of participants

Ethical clinical trials combine seeking answers to important questions with scientific validity and appropriate protection and respect for all involved, particularly participants. Independent review of proposals for new research, through an Institutional Review Board (IRB), Research Ethics Committee (REC) or equivalent, is an important governance tool and can help ensure appropriate steps are taken to protect the rights and welfare of participants.

Appropriate participant communication

Key Message: At all stages of a RCT (before, during and after), relevant, easily understandable information should be shared with trial participants, carefully balancing the duty to inform against the risk of information saturation and taking account of the clinical context. Information should be provided in a clear manner and in suitable languages and formats for the intended audiences.

Why this is important: Providing timely and relevant information to participants during a trial facilitates ethical research with benefits to both the participants and the quality of the trial results. It is essential that potential or recruited trial participants are appropriately informed but presenting excessive or exhaustive detail can work against this objective by overwhelming or confusing g potential participants. Care should be taken to communicate effectively and enable relevant discussion. The exact approach may be influenced by the context of the research, including clinical, cultural or other issues.

Relevant consent

Key Message: The trial consent process should clearly explain to potential trial participants the reasons or the trial, the questions it is seeking to answer, what is involved for them, and the potential benefits and risks of participation. The extent, nature and timing of information provided before and during the informed consent process should be guided by the level of additional risks and commitment that participation in the RCT would involve in the context of the usual clinical care or circumstances that the same individuals would normally receive. The information provided should prioritize the needs and expectations of the prospective participant rather than of the organization or individuals conducting the RCT. Consent information should be widely accessible and readily understandable, avoid legalistic or other technical language, and as succinct as possible. Approaches to obtaining and maintaining ongoing consent and communication should be relevant to the RCT it relates to.

Why this is important: Consent is valid if it is informed, voluntary, and competently given prior to entering the trial. There are some situations in which it is not possible for an individual to give informed consent (e.g. infants or individuals lacking mental capacity) or it is not practical to do so because of the urgency of the medical situation (e.g. trauma or medical emergencies). Such situations should not automatically preclude the conduct of RCTs (which may be the only way to provide reliable information on how best to manage such health issues) but appropriate safeguards should be put in place to maintain the rights of the individuals who participate. For some trials and in

some individual situations, explicit consent may be unnecessary. In such cases, there should be minimal additional risks and burdens to participation in comparison to the usual care a prospective participant might receive outside the trial.

Changing consent

Key Message: Participants should be free to stop or change the nature of their participation without affecting the usual care received, and effort should be made to determine the intended meaning of such individual decisions.

Why this is important: The term 'withdrawal' can mean different things to different people, ranging from participants wishing to stop receiving the study intervention, to stopping attending study visits in person (but perhaps be happy to be contacted or for information about their health outcomes to be collected from their regular doctors or from routine health data systems), to their biological samples no longer being assayed or stored, or their data no longer being processed or shared. Therefore, it is clearer to avoid the term and instead clarify with the participant(s) what level of participation they wish to have and what they want to cease. If this is not properly explored, and the 'withdrawal' is interpreted with prejudice to mean complete removal from the study, trial participants may be unnecessarily and inadvertently lost to full or partial follow-up, with possible implications for the reliability of trial findings, and may miss out on aspects of the RCT that matter to them (e.g. attendance at study visits or being informed about the progress and results of the study).

Implications of changing consent

Key Message: The rights of an individual participant to withdraw consent for use of trial data that has already been collected should be balanced with scientific and ethical requirements.

Why this is important: Removing data can result in unreliable or inconclusive findings, with ethical and clinical safety consequences for both participants continuing in the trial, and the care of future patients. (e.g. important safety signals may be missed.) It can be appropriate to make data which has already been collected available for analysis in order to demonstrate or preserve research integrity. Those involved in a trial and those whose care is influenced by its results should be able to be assured that the data are valid, and that they have not been modified through inadvertent, deliberate, or malicious means.

Managing the safety of individual participants in the RCT

Key Message: Detection and management of the safety of trial participants should be tailored to the trial population and to what is already known about the effects of the interventions. Such approaches may be modified as new information emerges (e.g. from other trials or clinical studies in the relevant population). In some circumstances it may be appropriate to exclude some groups of individuals from a trial if the likely risk to their health is excessive (compared with potential gain) and cannot be mitigated by reasonable clinical strategies. For some blinded trials, there may be occasions when knowledge of the allocated intervention for an individual participant could materially influence the immediate medical management of the participant. In such circumstances, it should be possible for the treatment allocation to be unblinded and disclosed to the relevant medical team without delay.

Why this is important: The procedures used to detect, investigate, and respond to unwanted health events for individual participants should be shaped by what is already known about the effects of the intervention from previous research or usage, as well as the background epidemiological and

clinical features of the intended trial population (e.g. their demographics, comorbidities, and concomitant intervention). If new information emerges during the course of the trial (e.g. from other studies or as a consequence of advice provided by the trial Data Monitoring Committee) then processes and procedures for managing the safety of individual participants should be reviewed and may need to be modified (e.g. changes in the nature and timing of assessments, training provided to trial staff, information provided to participants, or in the eligibility criteria for the trial).

Communication of new information relevant to the intervention

Key Message: During an ongoing trial, new information may become available (from within the trial or from external sources) which materially changes what is known about the effects of the intervention for some or all participants. This should be communicated to those involved in overseeing, conducting or participating in the clinical trial for whom it is relevant (e.g. because it might affect their understanding of the intervention or because they are required to take some action). Such communications and reports should be informative, timely and actionable.

Why this is important: Excessive, irrelevant or uninformative reports (particularly of individual cases) distract attention from those that require action. It is often preferable to produce and circulate contextualized periodic updates that are focused on safety issues that matter. Such reports may also be provided to the Data Monitoring Committee (for consideration in the context of the unblinded emerging trial data) and to regulatory bodies (for consideration of the implications for participants in other trials and for the wider group of patients and public). The distribution of reports should be in a format and timing that is commensurate with the action that is likely to be needed and the audience for which it is intended (e.g. participants, clinicians, regulators).

3. Good RCTs are collaborative and transparent

All those involved in RCTs share responsibility for building and sustaining the trust of collaborating partner organizations and clinical communities, participants, and the wider public. Trust is undermined when RCTs are not sufficiently relevant, fair, transparent, and respectful of the rights, interests, concerns, and values of all involved (especially those people who participate in them or whose care will be influenced by the results).

Working in partnership with people and communities

*Key Message***:** Potential participants and/or members of the relevant community provide valuable contributions to the design, execution and interpretation of RCTs.

Why this is important: The involvement of patients and relevant members of the public can play a key role in refining and prioritizing research questions; assessing RCT acceptability and feasibility; selecting of outcomes that are relevant and meaningful to the intended population; developing the RCT design and procedures; optimizing the nature and delivery of information; and encouraging dialogue about access to health interventions that prove effective. Working in partnership with people and communities is likely to increase trust and confidence, while decreasing the risk of important groups being excluded or the needs of local populations or sectors being overlooked or misunderstood.

Collaboration among organizations

Key Message: It is important that interactions between individuals in different organizations, including those in resource-rich and resource-poor settings and among commercial, academic and

healthcare sectors are fair and respectful of the interests, concerns and values of all involved, including trial participants and their communities. Working collaboratively with partners to consider which features of a RCT are critical to its quality, and supporting a delivery approach that is appropriate to the setting and context can enhance a trial's resilience and efficiency.

Why this is important: Collaborative working shares ideas and expertise, helps avoid misaligned approaches or substantially different priorities, and can maximise use of resources and increase efficiency.

Transparency

Key Message: Clinical trials should be registered from the outset on a publicly available trials database. Making other trial information (including the trial protocol and other trial documentation) public is strongly encouraged. Once the RCT is completed, trial reports should be publicly available in a timely manner (typically within 12 months) and should describe the study design, methods, and results in a clear and transparent manner. It can be helpful for such reports to be available in formats that permit both professional and lay readers to understand and interpret the results. Reporting results to participants and to the public requires different approaches to reporting results to the clinical and scientific community. Data sharing should be enabled at a suitable time if ethical, feasible, and scientifically appropriate.

Why this is important: Transparency and sharing of knowledge about health interventions help generate further knowledge, build and maintain trust, and give confidence both to those involved in the RCT and to those who are not. Timely communication of trial results (regardless of the findings) is vital to guide future research, reduce unnecessary duplication of effort which wastes resources, and enable care to be guided by an up-to-date evidence base. Good communication can also support wider efforts to foster potential collaborations and increase informed participation in RCTs.

4. Good RCTs are designed to be feasible for their context

Ensuring that a trial is set up to be practicable and produce reliable, actionable results is an important scientific and ethical duty. Consideration of the context and existing resources in a proposed trial setting can better inform effective trial design.

Setting and context

Key Message: The design and implementation of RCTs should recognize and be shaped by the characteristics of the settings in which they take place. These include the health needs and preferences of communities, their ability to access to health care, and their understanding of clinical trials, as identified through appropriate involvement, consultation and engagement with patients and the public.

Why this is important: These characteristics, alongside the nature and complexity of the research, are critical in identifying the ethical issues at stake and the issues, burdens, and benefits of running the RCT in that setting. Relevant and accessible RCTs are more likely to recruit a sufficient number of trial participants. Good patient and public involvement and education across the relevant communities help shape successful recruitment and subsequent adoption of the results.

Use of existing resources

Key Message: RCTs should be tailored to be practicable given the available infrastructure in relevant settings. This includes making optimal use of pre-existing resources and facilities, including utilizing any expertise, skills, professional standards, and quality oversight mechanisms associated with routine healthcare practice. While all individuals involved in performing a RCT should be qualified by education, training or experience to perform their respective task(s), it should be recognized that there are many aspects of delivering a clinical trial that are in line with routine care and therefore may not require additional training, procedures or checks.

Why this is important: RCTs should not be wasteful of staff and participants' time, use of interventional or other medical supplies, energy, or environmental resources. Where there are strengths and safeguards in routine systems, these should not be duplicated or altered without careful justification. The closer trial processes are to routine practice for participants and staff, the more efficiently and effectively they are likely to be delivered and the fewer mistakes they are likely to make, resulting in improved quality.

5. Good RCTs manage quality effectively and efficiently

Delivery of a high-quality trial requires competent decision-making and coordinated execution. Good governance and good trial quality management can help achieve these features.

Competent advice and decision-making

Key Message: RCTs should be subject to sufficient scrutiny to support the delivery of an informative, ethical and efficient study, and to avoid, correct, or mitigate problems.

Why this is important: Effective and efficient governance (example.g. through a Trial Steering Committee) helps to maintain the scientific and ethical integrity of a trial and advise on appropriate courses of action. It should be structured to enable effective response to issues that may arise, particularly when multiple organizations are involved, and enable reasonably consistent implementation across the trial

Membership of trial governance structures should reflect the expertise necessary to scrutinise key roles, responsibilities, and risks, and should build on the diverse strengths and capabilities of those involved. The need for a member or component of the governance structure to have independence from trial sponsorship and management should be determined by assessing the risk that judgement and advice could be materially influenced (or perceived to be influenced) by the relationship.

Governance approaches should account for the opportunity cost of associated activities by considering the extent to which they might impede participants and communities from benefiting from an effective intervention or prolong the time an ineffective or hazardous intervention is used. Prolonged or excessive governance activities, which drive up unnecessary costs, deter trial designs of sufficient size or duration, or discourage clinicians and participants from being involved should be avoided.

Protecting trial integrity

The integrity of trial results should be protected by ensuring that decisions about trial design, delivery and analysis are not influenced by premature access to unblinded information about the emerging results.

Planning for success and focusing on issues that matter

Key Message: Good quality should be prospectively built into the design and delivery of RCTs, rather than relying on retrospectively trying to detect issues after they have occurred (when often they cannot be rectified). RCTs should be described in a well-articulated, concise, and operationally viable protocol which is tailored to be practicable given the available infrastructure in relevant settings.

Why this is important: Rather than trying to avoid all possible issues, the aim should be to identify the key issues that would have a meaningful impact on participant well-being and safety or on decision-making based on the trial results. Efforts can then be focused on minimizing, mitigating, and monitoring those issues. Such an assessment should consider the context of the RCT and what is additional or special about it by comparison with routine care. Broadly, these considerations come under four headings:

- *factors associated with the intervention* (e.g. known and potential adverse effects; comorbidities or concomitant medications that might impact safety; special requirements for administering the intervention)
- *factors associated with evaluations required to answer the study objective that would not be expected in usual care* (e.g. additional invasive investigations)
- *resource implications* (e.g. need for specialist imaging or laboratory assays; unfamiliar or novel procedures requiring additional training)
- *ethical and privacy implications* (e.g. access to medical records and sharing of health information with pharmaceutical companies, researchers, or regulators)

Such an assessment process can then be used to guide the development of error mitigation approaches such as standard operating procedures, training, and trial monitoring. Trial processes that add scientific or ethical value to RCTs should be prioritized, and those that do not, or where the additional complexity outweighs the benefit should be avoided**.**

Monitoring, auditing and inspection of study quality

Key message: The nature and frequency of any trial monitoring, auditing and inspection activities should be proportionate to any identified risks to study quality.

Why this is important: Good trial monitoring, auditing and inspection activities identify issues that matter (important deviations from the protocol or unanticipated issues that threaten to undermine the reliability of results or protection of participants' rights and wellbeing) and provide an opportunity to further improve quality (e.g. through modifications to the protocol and procedures, training and mentoring staff, or information provided to participants). Excessive monitoring, auditing and inspection activities and failure to focus on details that have a material impact on trial quality wastes resources, creates distraction, and demotivates staff.

Rational monitoring focuses on the issues that will make a material difference to the participants in the trial and the reliability of the results (e.g. trial recruitment, adherence to allocated intervention, blinding, and completeness of follow-up). It informs corrective actions, supports staff, and enables improvements. It is important not to confuse more documentation for better quality. Example approaches that may be used include central review (including statistical analysis) of trial data and performance metrics to assess performance of staff and sites, in person or virtual support and mentoring for trial staff (e.g. through observation of study visits, with participant consent), and visits to clinical trial sites and facilities.

Regulatory, auditing or inspection requirements should be proportionate and sensitive to the scientific and ethical qualities and objectives of a RCT. They should recognise the opportunity-cost of, and avoid, setting irrelevant or disproportionate requirements that might discourage the conduct or participation in good RCTs that are designed to address important questions.

Conclusion

RCTs play a central role in generating the evidence needed to inform the development and implementation of interventions to improve health. In promoting the unique benefits of randomization, this guidance is promoting methodology that – when implemented effectively – answers questions reliably.

Investing in and adhering to the principles of this guidance will strengthen the scientific and ethical quality of any RCT. This guidance endeavours to recognize that the application of these principles will look different from trial to trial. However, the essential goals remain the same and a good trial will apply all the principles wisely. By supporting the key messages with explanations of their importance, the guidance can act as a tool to both prompt and justify the tailored application of the principles in a particular trial or setting.

It is important to recognize and challenge barriers to implementing the principles of this guidance. Clinical trials need robust systems and administrative functions to succeed but these same systems and administrative functions can fail to facilitate – or even deter – pursuit of the principles of good RCTs to the detriment of individual and public health and well-being.

If this guidance helps the clinical trials community to develop, fund, participate in, run, regulate and utilize good trials more effectively, it will have been successful. However, the authors welcome recommendations for modification or refinement based on experience of use.

Please send commentary to contact@goodtrials.org for consideration in future work of the Good Clinical Trials Collaborative.

Guidance Development

Good Clinical Trials Collaborative Secretariat

- Martin Landray | Senior Lead
- Nick Medhurst | Team Lead
- Charlie Rowley | Project Manager
- Nana Shimosako | Project Manager
- Alice Barney | Coordinator
- Aisha Mazhar | Officer
- Isabel Smith | Officer

with special thanks to

- Christina Reith | Nuffield Department of Population Health, University of Oxford

Good Clinical Trials Collaborative Steering Group

- Rob Califf | formerly Verily Life Sciences and Google Health
- Mimi Darko | Food And Drugs Authority, Ghana
- Jim Elliott | UK Health Research Authority
- Jeremy Farrar | Wellcome Trust
- Ian Hudson | Bill & Melinda Gates Foundation
- Dorcas Kamuya | KEMRI-Wellcome Trust Research Programme
- Kathryn Maitland | KEMRI-Wellcome Trust Research Programme
- Vasee Moorthy | World Health Organization
- Amrit Ray | Biohaven Pharmaceuticals
- Nancy Roach | Fight Colorectal Cancer
- Soumya Swaminathan | World Health Organization
- Fergus Sweeney (Observer) | European Medicines Agency
- Janet Woodcock (Observer) | U.S. Food & Drug Administration

Acknowledgements

The work of the Good Clinical Trials Collaborative has been made possible by generous grants from the Bill & Melinda Gates Foundation and the Wellcome Trust.

In acknowledging the contributions of the individuals named below, we do not claim their endorsement of the guidance but wish to express our gratitude for having volunteered their expertise and time towards its development.

- John H. Alexander | Duke Clinical Research Institute, Duke University
- Susana Almeida | Medicines for Europe
- Frank E. Baiden | Department of Clinical Research, London School of Hygiene and Tropical Medicine
- Sunita Sheel Bandewar | Vidhayak Trust; Health, Ethics and Law Institute of FMES
- Trishna Bharadia | Independent Patient Advocate
- Barbara E. Bierer | Brigham and Women's Hospital, Harvard Medical School
- Anders Bjartell | Skåne University Hospital and Lund University
- Gillian Booth | University of Leeds
- Devi Leena Bose | International AIDS Vaccine Initiative (IAVI)
- Louise Bowman | Nuffield Department of Population Health, University of Oxford
- Marc Buyse | International Drug Development Institute (IDDI), Louvain-la-Neuve, Belgium

- Marina Cardozo Vasco, PhD | Flutter Innovation
- Nichapa Choengsamor | DSIL Global
- Adam Cohen | Leiden University Medical Centre
- Sarah Collen | European Association of Urology
- Rory Collins | Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), University of Oxford
- Sabrina Comic-Savic | Trialspark
- Janet Darbyshire | University College London
- PJ Devereaux | McMaster University
- Martin Dreyling | LMU University Hospital, Department of Medicine III
- John Eikelboom | David Braley Cardiac Vascular and Stroke Research Institute, Hamilton Health Sciences, McMaster University
- M. Khair ElZarrad (Observer) | CDER - U.S. Food & Drug Administration
- Ezekiel J. Emanuel | Department of Medical Ethics and Health Policy, Perelman School of Medicine, University of Pennsylvania
- Jonathan Emberson | Nuffield Department of Population Health, University of Oxford
- Marcela Fajardo-Moser | ERA-EDTA
- Andrew J. Farmer | NIHR Health Technology Assessment Programme
- Barbara Farrell | UK Trial Managers' Network
- Dean A. Fergusson | Ottawa Hospital Research institute
- Morenike Oluwatoyin Folayan | Faculty of Health Science, Obafemi Awolowo University, Ile-Ife, Nigeria
- Alan G Fraser | Cardiff University
- Janet Frost | Independent Adviser
- Christian Gisselbrecht | European Hematology Association
- Jennifer Harris | Association of the British Pharmaceutical Industry
- Richard Haynes | MRC Population Health Research Unit and Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford
- Chris Hayward | Peninsula Clinical Trials Unit, University of Plymouth
- J.M. den Heijer | Centre for Human Drug Research, Leiden
- Kaustubh Joag | Centre for Mental Health Law & Policy, ILS, Pune
- Pichet Kamolrungsantisuk | Medical Research Network for Social, Medical Research Foundation Thailand
- Evelyne Kestelyn | Oxford University Clinical Research Unit (OUCRU)
- Patricia Kingori | Nuffield Department of Population Health, University of Oxford
- Carol Knott | Nuffield Department of Population Health, University of Oxford
- Denis Lacombe | European Organisation for Research and Treatment of Cancer
- Trudie Lang | The Global Health Network, University of Oxford
- Roger J. Lewis | Berry Consultants, LLC, Austin, Texas
- Anne S Lindblad | formerly The Emmes Company LLC
- Amalee McCoy | Independent
- Maisie McKenzie | Patient and Public Involvement and Engagement Adviser
- Georgina McMasters | Independent Lay Adviser
- Ann Meeker-O'Connell | formerly Vertex Pharmaceuticals
- Usha Menon | MRC Clinical Trials Unit, Institute of Clinical Trials & Methodology, University College London
- Janet Messer | Health Research Authority
- Hamid Moradi | Associate Clinical Professor
- Neetha Shagan Morar | HIV Prevention Research Unit, South African Medical Research Council (HPRU, SAMRC)
- Briggs W. Morrison |Independent
- Henry Mwandumba | Malawi Liverpool Wellcome Clinical Research Programme
- Della Ogunleye | Independent Lay Adviser
- Martin O'Kane | MHRA
- Deepa Pandit | Centre for Mental Health Law and Policy, Indian Law Society, Pune

- Michael Parker | Ethox Centre, Nuffield Department of Population Health, University of Oxford
- Nicola Perrin | Independent
- Nittaya Phanuphak | Institute of HIV Research and Innovation (IHRI)
- Sheuli Porkess | Actaros
- Ian Roberts | LSHTM
- John Roberts | Independent Lay Adviser
- Sara Román Galdrán | European Hematology Association
- Michel Satya Naslavsky | Human Genome and Stem Cell Research Center, Biosciences Institute, University of São Paulo
- Daniel I. Sessler | Michael Cudahy Professor & Chair, Department of Outcomes Research, Cleveland Clinic
- Rachit Shah | Quicksand Design Studio Pvt. Ltd
- Joseph Skhosana | Independent
- Natalie Staplin | Nuffield Department of Population Health, University of Oxford
- Kannan Subramaniam Viatris
- Jeremy Sugarman | Harvey M. Meyerhoff Professor of Bioethics and Medicine, Berman Institute of Bioethics and School of Medicine, Johns Hopkins University
- Matthew R Sydes | MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology & BHF Data Science Centre with HDR UK
- Wojciech Szczeklik | Jagiellonian University Medical College, Krakow
- Pamela Tenaerts | Medable (formerly Clinical Trials Transformation Initiative)
- Shaun Treweek | Health Services Research Unit, University of Aberdeen
- Catherine Wandie | Matchboxology
- Christoph Wanner | European Renal Association-European Dialysis and Transplantation Association
- Tanyaporn Wansom | Independent
- Nicholas J White | Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok
- Scott Williams | Independent
- Janet Wittes | WCG Statistics Collaborative