



# **Guidance for Good Randomized Clinical Trials**

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**Developed by the Good Clinical Trials Collaborative**

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## Contents

1	Introduction.....	3
2	The role of randomized controlled trials in improving health .....	3
3	Guidance development .....	3
4	Objective.....	4
5	Scope .....	4
6	How to use this guidance .....	4
7	Principles of Good Randomized Controlled Trials.....	5
8	1. Good RCTs are designed to produce scientifically sound answers to relevant questions .....	5
9	Appropriate trial population.....	5
10	Robust intervention allocation .....	5
11	Adequate size .....	6
12	Blinding and masking of allocated trial intervention .....	6
13	Adherence to allocated trial intervention .....	7
14	Completeness of follow-up .....	7
15	Relevant measures of outcomes .....	7
16	Proportionate, efficient and reliable capture of data .....	8
17	Ascertainment of outcomes .....	8
18	Statistical analysis.....	9
19	Assessing beneficial and harmful effects of the intervention .....	9
20	Monitoring emerging information on benefits and harms .....	10
21	2. Good RCTs respect the rights and well-being of participants .....	11
22	Appropriate participant communication.....	11
23	Relevant consent .....	11
24	Changing consent .....	12
25	Implications of changing consent .....	12
26	Managing the safety of individual participants in the RCT.....	12
27	Communication of new information relevant to the intervention .....	13
28	3. Good RCTs are collaborative and transparent .....	13
29	Working in partnership with people and communities.....	13
30	Collaboration among organizations .....	13
31	Transparency .....	14
32	4. Good RCTs are designed to be feasible for their context.....	14
33	Setting and context.....	14
34	Use of existing resources.....	15

35	5. Good RCTs manage quality effectively and efficiently .....	15
36	Competent advice and decision-making .....	15
37	Protecting trial integrity .....	15
38	Planning for success and focusing on issues that matter .....	16
39	Monitoring, auditing and inspection of study quality .....	16
40	Conclusion .....	17
41	Guidance Development .....	18
42	Acknowledgements .....	18

## 43 Introduction

### 44 The role of randomized controlled trials in improving health

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

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

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

### 60 Guidance development

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

## 73 Objective

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

78 This new guidance has been developed to be:

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

## 88 Scope

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

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

## 109 How to use this guidance

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

## 114 Principles of Good Randomized Controlled Trials

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

### 119 1. Good RCTs are designed to produce scientifically sound answers to relevant 120 questions

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

127 This requires the combination of:

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

137 Good RCTs should include the following features:

#### 138 **Appropriate trial population**

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

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

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

#### 151 **Robust intervention allocation**

152 *Key Message:* Randomization requires generation of an unpredictable allocation schedule with  
153 concealment of which intervention will be allocated to a particular participant until after the point of

154 randomization. It should be impossible to predict in advance which individual trial participant or  
155 individual cluster (e.g. hospital or city in a cluster RCT) the study intervention is likely to be allocated  
156 to, so that investigators, health care providers and other staff involved, and potential participants are  
157 not aware of the intervention to which they will be assigned.

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

### 167 **Adequate size**

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

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

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

### 185 **Blinding and masking of allocated trial intervention**

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

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

197 routine clinical databases and disease registries). These considerations are important for both the  
198 assessment of both the efficacy and the safety of the intervention, including processes relating to  
199 adjudication of outcomes and considerations of whether an individual health event is believed to  
200 have been caused by the intervention.

### 201 **Adherence to allocated trial intervention**

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

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

### 210 **Completeness of follow-up**

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

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

### 224 **Relevant measures of outcomes**

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

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

**238 Proportionate, efficient and reliable capture of data**

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

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

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

**264 Ascertainment of outcomes**

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

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



279 **Statistical analysis**

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

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

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

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

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

319 **Assessing beneficial and harmful effects of the intervention**

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

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

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

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

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

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

#### 349 **Monitoring emerging information on benefits and harms**

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

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

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

366 evidence to suggest a change in the protocol or procedures, including cessation of one or more  
367 aspects of the trial. Such changes may be due to evidence of benefit or harm or futility (where  
368 continuing the trial is unlikely to provide any meaningful new information). In making such  
369 recommendations, a DMC should take account of both the unblinded analyses of the RCT and  
370 information available from other sources (including publications from other trials).  
371

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

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

### 378 **Appropriate participant communication**

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

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

### 390 **Relevant consent**

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

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

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

#### 412 **Changing consent**

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

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

#### 427 **Implications of changing consent**

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

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

#### 437 **Managing the safety of individual participants in the RCT**

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

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

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

### 457 **Communication of new information relevant to the intervention**

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

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

472

### 473 **3. Good RCTs are collaborative and transparent**

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

#### 479 **Working in partnership with people and communities**

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

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

#### 490 **Collaboration among organizations**

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

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

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

## 501 **Transparency**

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

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

518

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

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

### 523 **Setting and context**

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

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

### 533 **Use of existing resources**

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

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

### 547 **5. Good RCTs manage quality effectively and efficiently**

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

#### 551 **Competent advice and decision-making**

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

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

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

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

#### 571 **Protecting trial integrity**

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

## 575 **Planning for success and focusing on issues that matter**

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

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

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

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

## 600 **Monitoring, auditing and inspection of study quality**

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

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

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



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

622

## 623 **Conclusion**

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

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

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

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

641 Please send commentary to [contact@goodtrials.org](mailto:contact@goodtrials.org) for consideration in future work of the Good  
642 Clinical Trials Collaborative.

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