MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

So, you think you want to run a Randomised Controlled Trial?

Do you know what is meant by: "blinding", "stratified randomisation", "intention-to-treat analysis", "surrogate outcomes", "generalisability", "confounding factors", "cross-over trial"? If not, then you'd better read on...

First question to ask yourself – Do you really need to do a randomised controlled trial (RCT)?

*"Randomised controlled trials are the most rigorous way of determining whether a **cause-effect relation** exists between treatment and outcome and for assessing the cost effectiveness of a treatment."*[1]

- Do you have a clear study question? Use the PICO method (Population, Intervention, Comparison, and Outcome) to state your question.
- Does the answer already exist to the question you are planning to study? Make sure you have done a thorough literature search on the subject to see what is already out there. Remember; *"it is unethical to expose humans **unnecessarily** to the risks of research"*[2]
- Discuss your idea with colleagues/experts and determine whether the question is relevant and important for our patients and for MSF. Does it produce new, useful information? Does it have implications for our programmes? Does it have policy implications? Is it a priority area for MSF? Is the research feasible?
- Are you planning to study an "intervention" (e.g. a therapy, diagnostic test, surgical procedure) against a "**control**" (i.e. placebo or best available treatment)? Will you practically and ethically be able to **randomise** patients? (randomly allocate patients to different treatments). Or will you just **observe** different procedures or treatments?
- Is an RCT the **most appropriate** design to answer your specific research question, or would another kind of trial e.g. cohort study, case control study, cross-sectional study, be more appropriate? (See the Health Knowledge website[3] and Mann's paper[4] for a description of different study designs to help you decide).
- Do you have enough help and support? An RCT will only produce valid results if it is performed with rigorous methods. A properly run RCT will involve a number of people with a range of special skills e.g. Pharmacists, Statisticians, Epidemiologists, Data managers, etc. And remember you will also need access to a population of patients who are willing to be involved in your study and will be available for follow-up over the length of your study.
- Are you ready to commit the substantial time and personal resources needed to do an RCT?

Preparing to run a Randomised Controlled Trial (RCT)

Planning, more planning and preparation – Designing your study

*"Given that poor design may lead to biased outcomes, trialists should strive for **methodological rigour** and report their work in enough detail for others to assess its quality"*[1]

Time planning your RCT, checking your plans with other people (colleagues, experts, medical coordinator/specialist) will be time **well spent**. If you get to the end of your trial and realise that you haven't measured one variable in your patients that will give you the answer to a key question, you will have wasted a lot of time and resources.
The way to avoid this is to spend enough time at the beginning of the process PLANNING: think of all the possible aspects of the population, disease, therapy/ intervention, to be studied and think about practicalities such as what resources are available and the training of the staff you will be asking to carry out the study. Obviously this will be easier if you ask other people for help: eg, your local research support unit (if available), those who have been involved in RCTs before, people who work in the area you are studying and the staff who will be involved in running your trial. Ask fellow researchers and check what others have done (look for published manuscripts, design papers, or even trial protocols). YH Chan suggests spending 1/3rd of the total time of the study on planning your trial (Figure).[5]

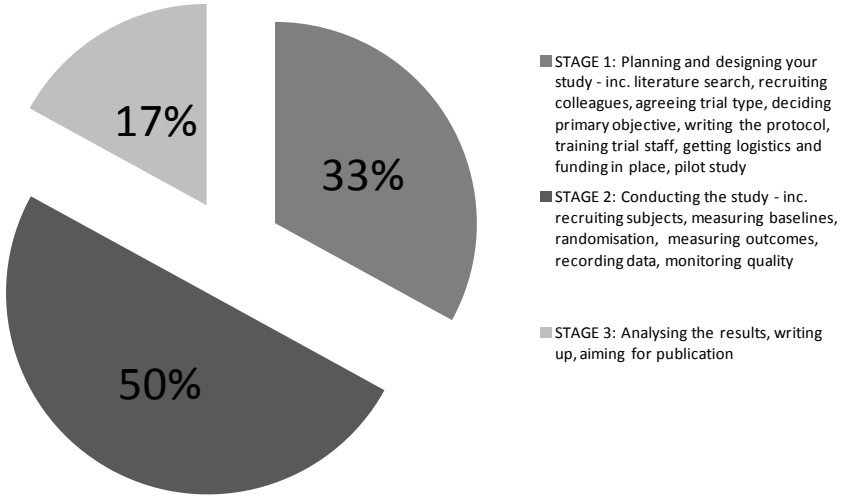

Figure: suggested percentage of time contribution for each stage of the research process (adapted from 5)

*"A **poorly designed**, poorly conducted and poorly reported trial is a violation to the rights of the subjects who gave consent to participate in a study; this is not ethical"*[5]

STAGE 0 – selling the idea:

Write a concept paper that includes the problem, relevance, objectives, hypothesis (and sub-hypotheses), main background (brief literature review), methods (rough), collaboration, budget, site. Get decision makers on board, including the field team at the site where you plan to do the research. Once you have a concept paper approved by the Medical Director of your section, you are ready to move on to the next stage, writing your protocol.

STAGE 1 – planning your trial:

1. State clearly the aims and objectives of your trial. Distinguish between primary and secondary objectives.
2. Decide on the **hypothesis** your study will test. *"Good hypotheses are **specific** and formulated **in advance** of commencement (a priori) of the study".*[6] The SMART criteria[7] can help you to check your hypothesis is clear (Specific, Measurable, Attainable, Relevant, Time bound). E.g. treating children under 5 with X disease (defined by fever over 39^{O}C, Blood Pressure, rash) with a dose of 600mg of drug X, twice a day for 10 days, will improve clinical outcomes – short term (2 weeks) and long term (6 months) – compared to "current best available treatment" (you will also need to explain how you will be able to tell that clinical outcomes are improved and also explain what the "current best available treatment" is). Are you looking for superiority against a placebo? Or do you want to state equivalence against a standard treatment? Remember that the hypothesis is crucial as it will determine the design and analysis of your study.
3. Are you planning to study a **significant** problem, is it relevant to the population you are working with? Have you consulted with the community to determine whether the research question is a shared concern? Will it be generalisable to other populations? i.e. will the results of your study be useful to people working in other communities/hospitals/situations? Or is it very peculiar to your site? *"the subject to be addressed should be of clinical, social or economic significance to afford **relevance** to the study"*[6]

4. Have you done a thorough **literature review** so that you know what has already been discovered in this area and what has been tried and failed? This will help you refine your hypothesis.
5. **Operational considerations** must be weighed. The impact of the research on the MSF project must be assessed and the research planned with the support and knowledge of field staff. It should be built into a project's Annual Plan and added to the sectional Research Agenda.
6. **Colloborative Partnership: As part of MSF's Ethical Framework, efforts should be made to collaborate with local partners and research institutes to build capacity, and ensure responsibility and ownership of the study and the study results. This partnership should be established early, in order to have the input of local researchers in protocol development.**
7. Consider whether you need to run a **pilot study** (a small-scale version) before your trial. If so this needs to be included in the protocol and is subject to ethics review. After the pilot you will need to refine your trial methods appropriately, adjust the protocol, and ensure ethics review is obtained for the adjusted version.[6]
8. Define your **primary and secondary outcomes** that match your aims and objectives – what will you measure in your participants to determine that you have a clinically meaningful improvement (or worsening) that may be due to your intervention? What will be the primary outcomes that will help you evaluate your hypothesis? (e.g. weight gain after 4 weeks). Will there be other outcomes that you want to measure to help you answer your questions? (e.g. upper arm measurement). Strictly define all outcomes and how they will be measured. Remember to assess all relevant **baseline measures**. Decide how often and when to measure for changes
9. A decision must be made on what constitutes **(serious) adverse events and reactions** and a plan of action if they occur.
10. **Define your target population** and decide **how you will recruit** a representative sample to your study population to make your results as generalisable as possible. Who will be included in the study? E.g. children under 5 years admitted to Hospital X children's ward with disease Y between April and Sept 2011. Do you have **exclusion criteria**? (e.g. exclude from the study if allergy to drug X or severe malnutrition or taking part in other study). Remember that in many trials recruitment is slower and more difficult than anticipated. Define who will be in your analysis: ie, whether per protocol (includes only those patients who completed the treatment originally allocated. If done alone, this analysis leads to bias) or intention to treat analysis = *"Patients are analysed within the group to which they were allocated, irrespective of whether they experienced the intended intervention"*[6]
11. How will you make sure that you can obtain ***informed* consent** from all trial participants? Consider language and local/cultural issues when obtaining consent. Will you give compensation for their time/travel to the participants, and how often, and in what form? Are the participants children, if so is there a caretaker who is legally permitted to authorise consent?
12. **Sample size calculation**. Involve a statistician or epidemiologist! You need to know how many participants you will need to include in your trial to obtain statistically significant results. This will influence the design, duration and **costs** of your trial.
13. Work out how you will **randomise** your participants. There are different ways you can randomly allocate your patients to different arms of the study (e.g. stratified, or clustered). A statistician or epidemiologist can easily do it, but it needs to be done properly to reduce the chance of bias and confounding in your results.
14. Who can be blinded in your study? Are you going to be able to **blind** the participants? The staff who administer the intervention (double blinding)? The staff who measure the outcomes? The people who analyse the data? Is it ethical/practical to blind everyone? Can you arrange rapid **unblinding** in case of emergency?
15. Clearly define the intervention(s) you want to test. When, how, how much should be given.
16. If **comparison of drugs is involved**, you (with the assistance of your pharmacy department) will need to look for an appropriate producer, get an agreement and contract.
17. What will be your **control** intervention? Is there a current treatment that you are comparing the new intervention against? Do you need to produce a placebo that looks the same as your intervention? If you are using blinding then you will need to **make sure that all treatments look the same** to both patients and staff treating the patients. If comparing drugs, you need to make sure your pharmacy department can help.
18. **Data management:** How will data be **collected** – Will you use paper forms? An electronic database? Who will transcribe data from form to database and how will you ensure that errors are minimised? Will you use an existing electronic database or do you require a new database? Do you need a 3-dimensional or 2-dimensional database (eg Excel)? **Data quality** - who will do data entry, what supervision is required, what quality checking and data cleaning (double data entry? field limits, cross checking entries with raw data?) **Backup** of databases - where will they be kept, how often will they be backed up? Who will have access to the data and electronic databases? **Long-term storage** of raw and electronic data: in clinical trials especially if of a new drug or diagnostic, data must be kept for a minimum of 3 years and often more. Where will electronic records be safely

stored ensuring protection of confidentiality? If there are paper data collection forms arrangements are needed for these to be boxed and sent back to Amsterdam/relevant operational centre.

19. Are you going to pre-plan **interim analyses** of your results and appoint an independent data monitoring committee (DMC)?[89] If your trial is long and assesses a severe outcome (e.g. death) it is especially important to look at your data at intervals before the end of the trial. An independent DMC can review your results regularly and give advice if necessary – e.g. a change in the protocol may be needed, the trial may need to be stopped (for benefit or harm). You need to decide on the composition of the committee and define their roles.
20. Imagine what might be the **logistical issues** e.g. How will you recruit staff to help? In what specialties and at what stages of the trial? Other issues include training staff to run the trial identically in each centre, supply of drugs/treatment on time, getting access to the patients to make sure they receive the intervention and also when you need to measure the results. Do you need to factor in costs for transport (for staff or patients)? Are you going to treat people at the hospital or go out to their communities? And don't underestimate the effort needed to recruit and get consent from patients.
21. Develop **standard operating procedures** for the trial methodologies and quality control procedures. Make a TOR (terms of reference, an outline of their role) for the local person on your research team (this person represents his/her population and represents MSF back to the population), make a TOR for key functions (eg field research coordinator).
22. Make a **time line**, expected date of starting, recruitment rate, expected period of data gathering. Make a **budget**; review the budget before the start as inflation can change salaries and transport considerably.
23. Consider the **ethical issues** in your research. Our patients are usually extremely vulnerable and we have an obligation to ensure that research maximises benefit versus harm. It is important to follow the MSF Ethics Review Board (ERB) framework for assessing medical research in MSF.[10] In addition to scientific validity, informed consent, confidentiality and the harm-benefit ratio of proposed studies, it is important to ensure that the study population is engaged in a collaborative partnership (eg local researchers are included and the community is involved) and benefits fairly from any resulting rewards of research. The social value of proposed research is also important to weigh and mechanisms should be included to increase this (eg by dissemination of knowledge, ensuring access to drugs/treatments found effective, supporting the local health infrastructure).
24. How will your results be disseminated and used for advocacy? Publication is a first step but is NOT the most important aim of an RCT (or any other trial). Why do we carry out these costly and resource-intensive trials? To learn more about diseases and new treatment, to help decide if policies and guidance needs to be reviewed/ changed, to improve the lives of our patients. **Make sure the results of your study are USED!** Whether you prove or disprove your hypothesis, if your trial was well designed and you were studying a significant problem, then your results will be helpful to inform treatment locally, nationally or even internationally. So **make an advocacy plan** about how you are going to **let the right people hear about your results** (involve the public health department). Think about how to **disseminate** your results widely.
25. and after all that... **Write your protocol!**
    - Many good templates for protocols can be found on the internet. Three are listed below – references 11 (CONSORT), 12, 13 (NICE) are checklists specifically for RCTs.
    - Use the information gathered from all the above planning to write your protocol, which is an operations manual for your project. When writing this document, imagine that someone else may have to pick up the protocol and run the trial if you are unable to finish it (or if someone wants to repeat your study). Make sure the details of the 'Why?' and 'How?' the study is to be run are explained as well as the 'What?' is to be done. Describe, explain and define **all aspects** of the trial in **great detail**. Don't worry: this is not extra work. You will need all this information later when writing your report or publishing a manuscript about your results.

> *"[A comprehensive} study protocol will include: Aim and rationale of the trial; Proposed methodology/data collection; Definition of the hypothesis; Ethical considerations; Background/review of published literature; Quality assurance and safety; Treatment schedules, dosage, toxicity data etc."*[3]

    - The protocol should ideally be subjected to **peer review.** Involve different people to develop and review it (e.g. epidemiologist, medical experts, field staff, etc.).
    - All protocols should be reviewed by the relevant Medical Director.
    - It is also desirable to involve local researchers and/or Ministry of Health staff in the country where the study is located from the start, or at least to inform the Ministry of Health about the study.
    - The protocol must also undergo ethics review both in the country where the study is located and ethics review by the MSF ERB.
    - Trials must be registered at an appropriate registry (see list of registries14,15,16,17).

STAGE 2 – conducting your trial

26. **Setting up:** needs support from field programme site, and a person who understands research and is familiar with MSF's procedures to hire people, order supplies, etc.
27. **Recruit** patients**.**
28. Gain **informed consent**. Ensure the number of patients who refuse consent is recorded. Make sure you document all the numbers needed to be able to fill out the CONSORT Flow Chart [11; Appendix 1] regarding trial participants.
29. Collect **baseline measurements**, including all variables considered or known to affect the outcome(s) of interest.
30. **Randomise** study participants to treatment groups (new intervention vs. standard or placebo).
31. **Follow-up** all treatment groups uniformly, with assessment of outcomes continuously or intermittently.
    a. This means collecting information on those included and those excluded and reasons for exclusion, as well as number of people eligible but not asked or who refuse participation / refuse consent, drop-outs, withdrawals, and those lost to follow up.
    b. Try everything possible to avoid or minimize drop-outs/loss to follow-up, and missing data in general!
32. **Quality control:** Monitor compliance to the protocol and losses to follow-up. *"An inadequate approach to quality control will lead to potentially significant errors due to missing or inaccurate results."*[6] The field investigator will need to make sure that all the staff involved are motivated and given the training and equipment they need to carry out the trial – equally across all sites. If the trial is long or staff turnover high, training may need to be repeated. Implement quality control methods for the study procedures and data management as per protocol.
33. Check and regularly review that **severe adverse events** are being recorded according to protocol, and that the **DMC** is constituted according to protocol.

STAGE 3 – analysis and writing up

34. **Analysis** of your results – comparison of treatment groups.
35. **Interpretation** of the results (assess the strength of effect, alternative explanations such as sampling variation, confounding factors, bias).
36. **Feedback** results/reports to ethics committees and to the trial research site.
37. **Writing up** – following the CONSORT 2010 guidelines for parallel group RCTs[2] or the STARD criteria for trials investigating diagnostic tests.[18; Appendix 2]

*"CONSORT urges completeness, clarity and transparency of **reporting,** which simply reflects the actual trial design"*[2]

If you haven't contacted them before now, then now is the time to **call the Manson Unit** (medical unit) at MSF UK. The Medical Editor in the Manson Unit can assist you by editing your paper and helping you to get it published in the most appropriate journal.

38. **Publication** – hopefully.
39. **Dissemination of results and advocacy**. Follow your advocacy plan and make sure that your study results are used appropriately and reach the right audiences.

GOOD LUCK!

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Essential reading:

- A really easy to read (and short) paper explaining how to design an RCT: "Designing a research project: randomised controlled trials and their principles" by JM Kendall[6]
- "CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials"[2]

GLOSSARY OF TERMS	
Adverse event/serious adverse event	Any adverse change in health or side effect that occurs in a person who participates in a clinical trial while the patient is receiving the treatment (study medication, application of the study device, etc.) or within a previously specified period of time after the treatment has been completed. Adverse events categorized as "serious" (for example death, illness requiring hospitalization, events deemed life-threatening, or involving cancer or foetal exposure) must be reported to the regulatory authorities immediately, whereas minor adverse events are merely documented in the annual summary sent to the regulatory authority.
Arm	A group of patients receiving a particular treatment (or placebo) in a clinical trial. Any of the treatment groups in a randomized trial. Most randomized trials have two "arms," but some have three "arms," or even more.
Baseline	Information gathered at the beginning of a study from which variations found in the study are measured. i.e. before a participant starts to receive the experimental treatment which is being tested.
Bias	Systematic deviation of study results from the true results, because of the way(s) in which the study is conducted. Bias can be due to poor randomisation, or patients or investigator not being blind to the treatment.
Blinding/blinded	A trial is fully blinded if all the people involved are unaware of the treatment group to which trial participants are allocated until after the interpretation of results. This includes trial participants and everyone involved in administering treatment or recording trial results. Ideally, a trial should test (at the end) whether people can guess which group they have been allocated to. This is particularly important if, for example, one of the treatments has a distinctive taste or adverse effects.
Block randomisation	Block randomisation is a method used to ensure that the numbers of participants assigned to each group is equally distributed and is commonly used in smaller trials.
Cluster randomised controlled trial	One in which a group of participants are randomised to the same intervention together. Examples of cluster randomisation include allocating together people in the same village, hospital, or school. If the results are then analysed by individuals rather than the group as a whole bias can occur.
Cochrane database	An international collaborative project collating peer reviewed prospective randomised clinical trials.
Cohort	A group of individuals with some characteristics in common, e.g. a group of people born within the same period would be referred to as a birth cohort. A cohort may be identified so that one or more characteristic can be studied as it ages through time.
Confidence interval (CI)	The 95% confidence interval (or 95% confidence limits) would include 95% of results from studies of the same size and design in the same population. This is close but not identical to saying that the true size of the effect (never exactly known) has a 95% chance of falling within the confidence interval. If the 95% confidence interval for a relative risk (RR) or an odds ratio (OR) crosses 1, then this is taken as no evidence of an effect. The practical advantages of a confidence interval (rather than a P value) is that they present the range of likely effects.
Confounding factors	Factors that may affect the results of a trial as they can affect the outcomes measured in both arms.
Controls	In a randomised controlled trial (RCT), controls refer to the participants in its comparison group. They are allocated either to placebo or a standard treatment.
Cross sectional study	A study design that involves surveying a population about an exposure, or condition, or both, at one point in time. It can be used for assessing prevalence of a condition in the population.
Crossover randomised trial	A trial in which participants receive one treatment and have outcomes measured, and then receive an alternative treatment and have outcomes measured again. The order of treatments is randomly assigned. Sometimes a period of no treatment is used before the trial starts and in between the treatments (washout periods) to minimise interference between the treatments (carry over effects).

Double-blind	Refers to the fact that not only are the patients blinded, but also the people giving the treatment to the patients are blinded.
Drop-outs	Withdrawals and dropouts are those patients who fail to complete a course of treatment, or fail to report back on its outcome to the researchers. The reasons for doing so might be varied: the individuals may have moved away, abandoned the course of treatment, or died.
Eligibility criteria	A description of people that can (inclusion criteria) or cannot (exclusion criteria) take part in a trial.
Epidemiology	The branch of medical science that deals with the study of incidence and distribution and control of a disease in a population.
False positive	A test result that suggests that the subject has a specific disease or condition when in fact the subject does not.
Generalisability	The extent to which the findings of a clinical trial can be reliably extrapolated from the participants who participated in the trial to a broader patient population and a broader range of clinical settings.
Incidence	Is a rate and therefore is always related either explicitly or by implication to a time period. With regard to disease it can be defined as the number of new cases that develop during a specified time interval.
Inclusion criteria	Stated conditions which must all be met for a candidate to be included into a study.
Informed consent	The process of the patient learning what is involved in a clinical trial and then agreeing to take part, after having time to consider the implications and to have their questions answered.
Intention to treat (ITT) analysis	Analysis of data for all participants based on the group to which they were randomised and not based on the actual treatment they received.
Longitudinal study	A study that follows a group of patients over a period of time.
Lost to follow-up	When what happened to a participant cannot be ascertained even after active follow up efforts.
Meta-analysis	A review of the results of a large number of trials on a similar subject. A meta-analysis can be a particularly powerful research tool.
Multi-centre trial	A trial being carried out at more than one location.
Observational study	A study in which no intervention is made (in contrast with an experimental study). Such studies provide estimates and examine associations of events in their natural settings without recourse to experimental intervention.
Outcomes	Outcomes are the results that help to measure the effect of the intervention you are studying. Patient centred outcomes include mortality, morbidity, quality of life, ability to work, pain, etc. However, these are sometimes hard to measure within the confines of a trial so surrogate outcomes are used instead.
Peer review	A review of a trial's results by a group of independent experts.
Per protocol analysis	Per-protocol analysis is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated. If done alone, this analysis leads to bias.
PICO	Population, Intervention, Comparison, and Outcome (to state the research question in interventional studies).
Placebo	A substance given in the control group of a clinical trial, which is ideally identical in appearance and taste or feel to the experimental treatment and believed to lack any disease specific effects. In the context of non-pharmacological interventions, placebo is usually referred to as sham treatments. Placebo is not the same as giving no treatment and can induce real physiological changes.
Power	A study has adequate power if it can reliably detect a clinically important difference (i.e. between two treatments) if one actually exists. The power of a study is increased when it includes more events or when its measurement of outcomes is more precise.
Prevalence	Is not defined by a time interval and is therefore not a rate. It may be defined as the number of cases of a disease that exist in a defined population at a specified point in time.
Prospective study	Research in which a group of participants is identified, and then studied from that point

	forward in time. The opposite is a retrospective study.
Randomised trial	In a randomised trial, participants are allocated to receive one type of treatment or another by a random process, usually using a computer. This helps ensure the results are objective and unbiased.
Relative risk (risk ratio)	This is the ratio of the probability of developing the condition if exposed to a certain variable compared with the probability if not exposed.
Response rate	The proportion of participants who respond to either a treatment or a questionnaire.
Retrospective study	Research in which a group of participants is identified, and then studied from that point backward in time, usually via their medical records and interviews. The opposite is a prospective study.
Risk factor	A variable associated with a specific disease or outcome.
Sample size (n)	The number of individuals in a group under study. The larger the sample size, the greater the precision and thus power for a given study design to detect an effect of a given size.
Simple randomisation	For example, computer generated random number tables. Simple randomisation is rarely used.
Stratified randomisation	Stratified randomisation is used to ensure that important baseline variables (potential confounding factors) are more evenly distributed between groups than chance alone may assure. However, there are a limited number of baseline variables that can be balanced by stratification because of the potential for small numbers of participants within each stratum.
Surrogate outcomes	Surrogate measurements of effect are used as a substitute for real clinical outcome measures, or measured in parallel to such measures. They are often chosen as they can be quantified to produce statistical significance by studying a smaller population than would be needed to study the real clinical outcomes of actual overall morbidity or mortality. e.g. Blood pressure measurements as a surrogate for stroke, CD4+ T cell count in HIV infection as a surrogate for cellular viral load.
Variable	A value or quality that can vary between participants and/or over time

Appendix 1
*CONSORT 2010 checklist of information to include when reporting a randomised trial[2,11]

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Appendix 2
STARD checklist for reporting of studies of diagnostic accuracy[18]
(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	
Test methods	7	The reference standard and its rationale.	
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	
	13	Methods for calculating test reproducibility, if done.	
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	
	20	Any adverse events from performing the index tests or the reference standard.	
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	
	22	How indeterminate results, missing data and outliers of the index tests were handled.	
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	
	24	Estimates of test reproducibility, if done.	
DISCUSSION	25	Discuss the clinical applicability of the study findings.	

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