Different types of clinical evidence and study design

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The research question

What is a research question?

The researcher asks a very specific question and tests a specific hypothesis. Broad questions are usually broken into smaller, testable hypotheses or questions.

Often called an objective or aim, though calling it a question tends to help with focusing the hypothesis and thinking about how to find an answer

What makes a poor research question?

a question that matters to nobody, even you

hoping one emerges from routine clinical records

- the records will be biased and confounded
- they'll lack information you need to answer your question reliably, because they were collected for another reason

fishing expedition/data dredging – gathering new data and hoping a question will emerge

What makes a good question?

Feasible (answerable with a robust method)

Interesting

Novel

Ethical

Relevant

FINER criteria

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Real research questions

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RESEARCH

Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2-59 months in low resource settings: multicentre randomised controlled trial (SPEAR study)

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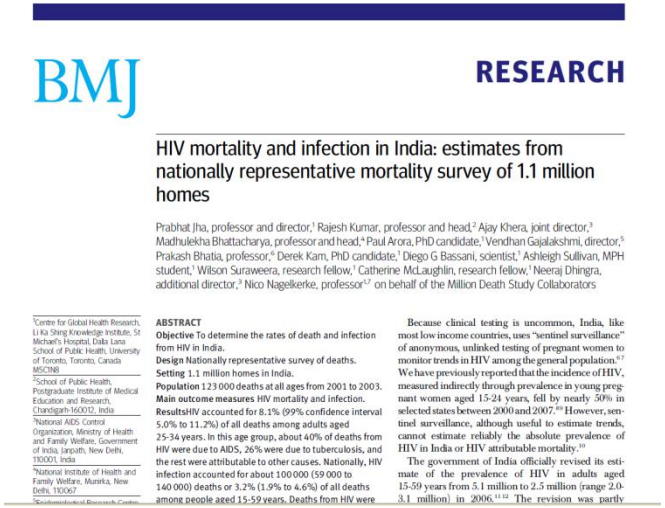
ABSTRACT

Objective To evaluate whether five days' treatment with injectable ampicillin plus gentamicin compared with chloramphenicol reduces treatment failure in children aged 2-59 months with community acquired very severe pneumonia in low resource settings.
Design Open label randomised controlled trial.
Setting Inpatient wards within tertiary care hospitals in Bangladesh, Ecuador, India, Mexico, Pakistan, Yemen, and Zambia.
predictors of treatment failure by multivariate analysis were hypoxaemia (oxygen saturation <90%), receiving chloramphenicol, being female, and poor immunisation status.
Conclusion Injectable ampicillin plus gentamicin is superior to injectable chloramphenicol for the treatment of community acquired very severe pneumonia in children aged 2-59 months in low resource settings.
Trial registration Current Controlled Trials ISRCTN39543942.



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RESEARCH

HIV mortality and infection in India: estimates from nationally representative mortality survey of 1.1 million homes

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ABSTRACT

Objective To determine the rates of death and infection from HIV in India.
Design Nationally representative survey of deaths.
Setting 1.1 million homes in India.
Population 123 000 deaths at all ages from 2001 to 2003.
Main outcome measures HIV mortality and infection.
Results HIV accounted for 8.1% (99% confidence interval 5.0% to 11.2%) of all deaths among adults aged 25-34 years. In this age group, about 40% of deaths from HIV were due to AIDS, 26% were due to tuberculosis, and the rest were attributable to other causes. Nationally, HIV infection accounted for about 100 000 (59 000 to 140 000) deaths or 3.2% (1.9% to 4.6%) of all deaths among people aged 15-59 years. Deaths from HIV were

Because clinical testing is uncommon, India, like most low income countries, uses "sentinel surveillance" of anonymous, unlinked testing of pregnant women to monitor trends in HIV among the general population.[1-7] We have previously reported that the incidence of HIV, measured indirectly through prevalence in young pregnant women aged 15-24 years, fell by nearly 50% in selected states between 2000 and 2007.[8,9] However, sentinel surveillance, although useful to estimate trends, cannot estimate reliably the absolute prevalence of HIV in India or HIV attributable mortality.[10]

The government of India officially revised its estimate of the prevalence of HIV in adults aged 15-59 years from 5.1 million to 2.5 million (range 2.0-3.1 million) in 2006.[11,12] The revision was partly

Is five days' treatment with injectable ampicillin plus gentamicin more effective than chloramphenicol in children under 5 with very severe pneumonia in low resource settings?

What is the prevalence of HIV infection in India, and how many premature deaths does it cause?

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How to focus your question

brief literature search for previous evidence

discuss with colleagues

narrow down the question – time, place, group

what answer do you expect to find?

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Turning a research question into a proposal

who am I collecting information from?
what kinds of information do I need?
how much information will I need? *
how will I use the information?
how will I minimise chance/bias/confounding?
how will I collect the information ethically?

* sample size – ask a statistician for help
http://www.bmj.com/collections/statsbk/13.dtl

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Minimising bias and confounding

Chance - measurements are nearly always subject to *random* variation. Minimise error by ensuring adequate sample size and using statistical analysis of the play of chance

Bias - caused by *systematic* variation/error in selecting patients, measuring outcomes, analysing data – take extra care

Confounding - factors that affect the interpretation of outcomes eg people who carry matches are more likely to develop lung cancer, but smoking is the confounding factor – so measure likely confounders too

Ethical issues – the wider aspects

what information to give before seeking consent?
deviation from normal clinical practice?
what full burden will be imposed on participants?
what risks will participants/others be exposed to?
what benefit might participants or others receive?
how might society/future patients benefit in time?
might publication reveal patients' identities?

Exactly what are you planning to do?

PICOS

P - who are the patients or what's the problem?

I - what is the intervention or exposure?

C – what is the comparison group?

O - what is the outcome or endpoint?

S – Sampling method? Sample size? Statistics? Study design?

More on PICO

Patients
- disease or condition
- stage, severity
- demographic characteristics (age, gender, etc.)

Intervention
- type of intervention or exposure
- dose, duration, timing, route, etc.

Comparison
- risk or treatment
- placebo or other active treatment

Outcome
- frequency, risk, benefit, harm
- dichotomous or continuous
- type: mortality, morbidity, quality of life, etc.

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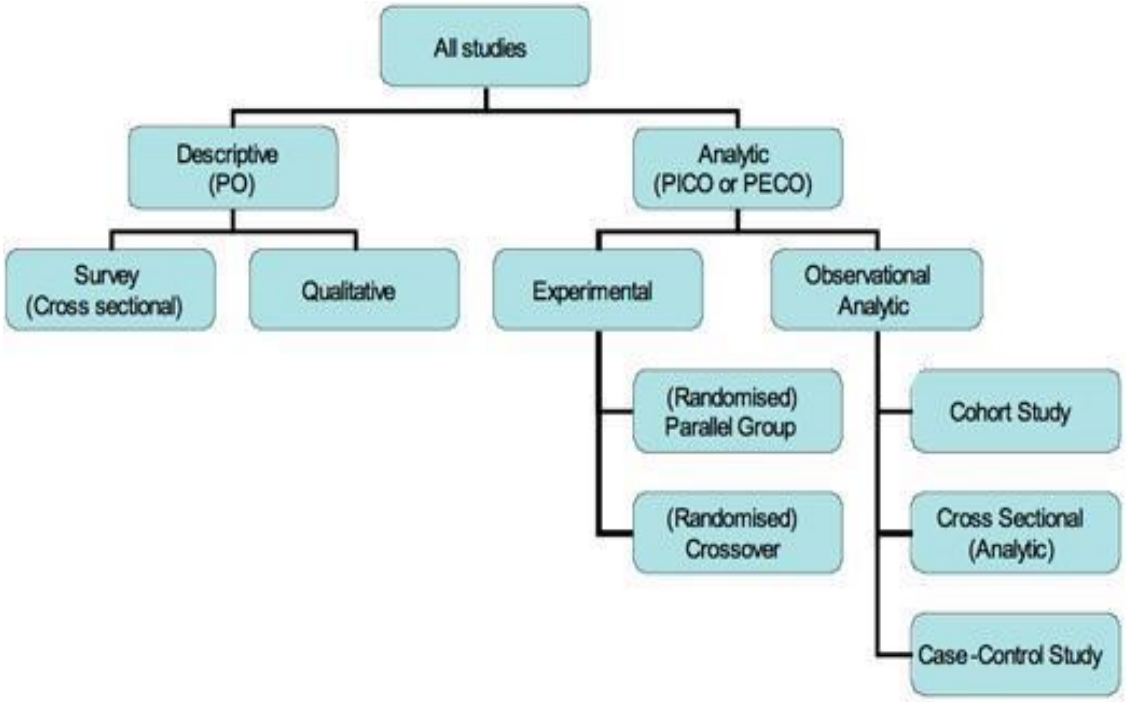
Study designs



Population (P) Outcomes (O)
Interventions (I) or Exposures (E)

Centre for Evidence Based Medicine, Oxford, UK www.cebm.net

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Are you going to observe or experiment?

observational – cross sectional, case series, case-control studies, cohort studies

- identify participants
- observe and record characteristics
- look for associations

experimental – before and after studies, comparative trials (controlled or head to head), randomised trials (ditto)

- identify participants
- place in common context
- intervene
- observe/evaluate effects of intervention

Pros and cons of the RCT

An experimental comparison study where participants are allocated to treatment/intervention or control/placebo groups using a random mechanism. Best for studying the effect of an intervention.

Advantages:

- unbiased distribution of confounders
- blinding more likely
- randomisation facilitates statistical analysis

Disadvantages:

- expensive: time and money
- volunteer bias
- ethically problematic at times

Pros and cons of crossover trial

A controlled trial where each participant has both therapies

e.g is randomised to treatment A first then starts treatment B.

Advantages:

- all participants serve as own controls and error variance is reduced, thus reducing sample size needed
- all participants receive treatment (at least some of the time)
- statistical tests assuming randomisation can be used
- blinding can be maintained

Disadvantages:

- all participants receive placebo or alternative treatment at some point
- washout period lengthy or unknown
- cannot be used for treatments with permanent effects

Pros and cons of cohort study

Data obtained from groups who have already been exposed, or not exposed, to the factor of interest. No allocation of exposure is made by the researcher. Best for studying effects of risk factors on an outcome.

Advantages:

- ethically safe
- participants can be matched
- can establish timing and directionality of events
- eligibility criteria and outcome assessments can be standardised

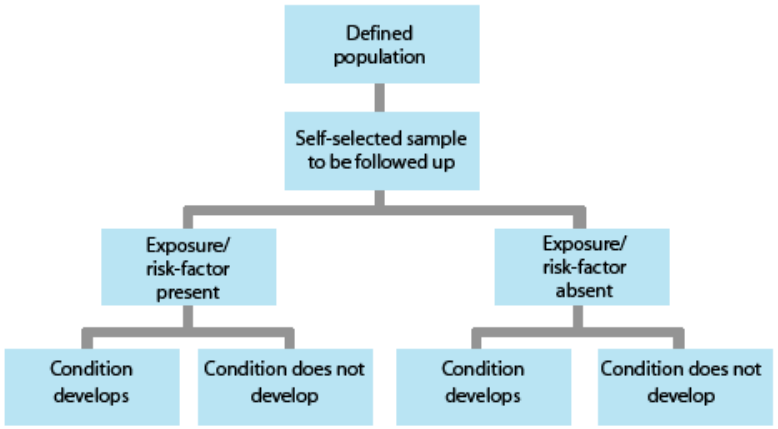
Disadvantages:

- controls may be difficult to identify
- exposure may be linked to a hidden confounder
- blinding is difficult
- for rare disease, large sample sizes or long follow-up necessary

Cohort study

Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: Prospective population based cohort study.

Di Angelantonio E, et al.
BMJ 341:doi:10.1136/bmj.c4986



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Pros and cons of case-control study

Patients with a certain outcome or disease and an appropriate group of controls, without the outcome or disease, are selected (usually with some matching) then information is obtained on whether the subjects have been exposed to the factor under investigation.

Advantages:

- quick and cheap as fewer people needed than cross-sectional studies
- only feasible method for very rare disorders or those with long lag between exposure and outcome

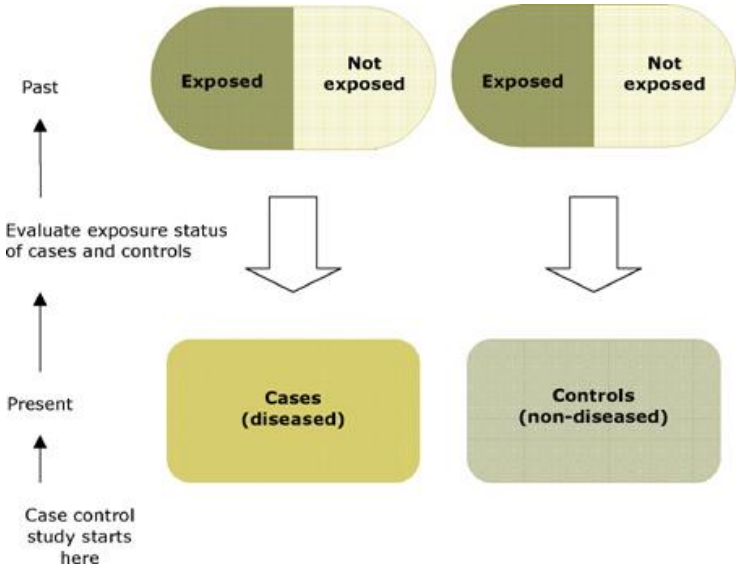
Disadvantages:

- reliance on recall or records to determine exposure status
- confounders
- selection of control groups is difficult
- potential bias: recall, selection

Case-control study

Effectiveness of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study.

de Palma O et al.
BMJ 340:doi:10.1136/bmj.c2825



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Pros and cons of cross sectional study

Examines the relationship between 1) diseases/other health related characteristics and 2) other variables of interest as they exist in a defined population at one time. Exposure and outcomes both measured at the same time. Quantifies prevalence, risk, or diagnostic test accuracy

Advantages:

- cheap and simple
- ethically safe

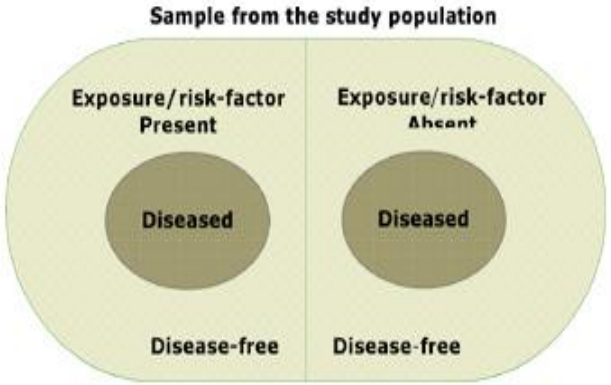
Disadvantages:

- establishes association at most, not causality
- recall bias, social desirability bias
- researcher's (Neyman) bias
- group sizes may be unequal
- confounders may be unequally distributed

Cross sectional study

Sociodemographic patterning of non-communicable disease risk factors in rural India: a cross sectional study.

Kinra S et al.
BMJ 341:doi:10.1136/bmj.c4974



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Reporting statements

CONSORT for randomised controlled trials

STARD for diagnostic accuracy studies

STROBE for observational studies

PRISMA for systematic reviews of trials

MOOSE for meta-analyses of observational studies

EQUATOR network

equator-network.org/resource-centre/library-of-health-research reporting/

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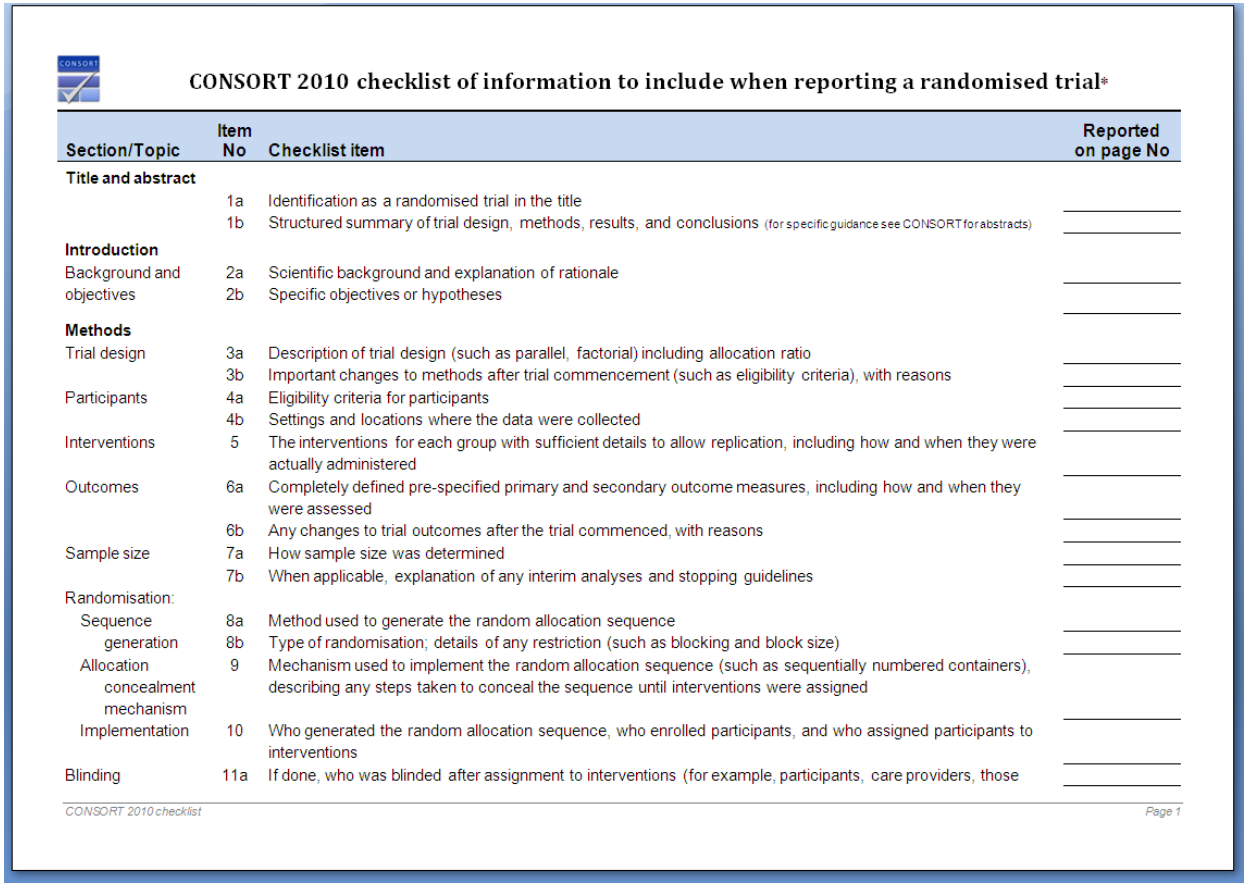
CONSORT 2010
CONsolidated Standards of Reporting Trials



CONSORT 2010 checklist of information to include when reporting a randomised trial*

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	

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CONSORT 2010 cont.

		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.

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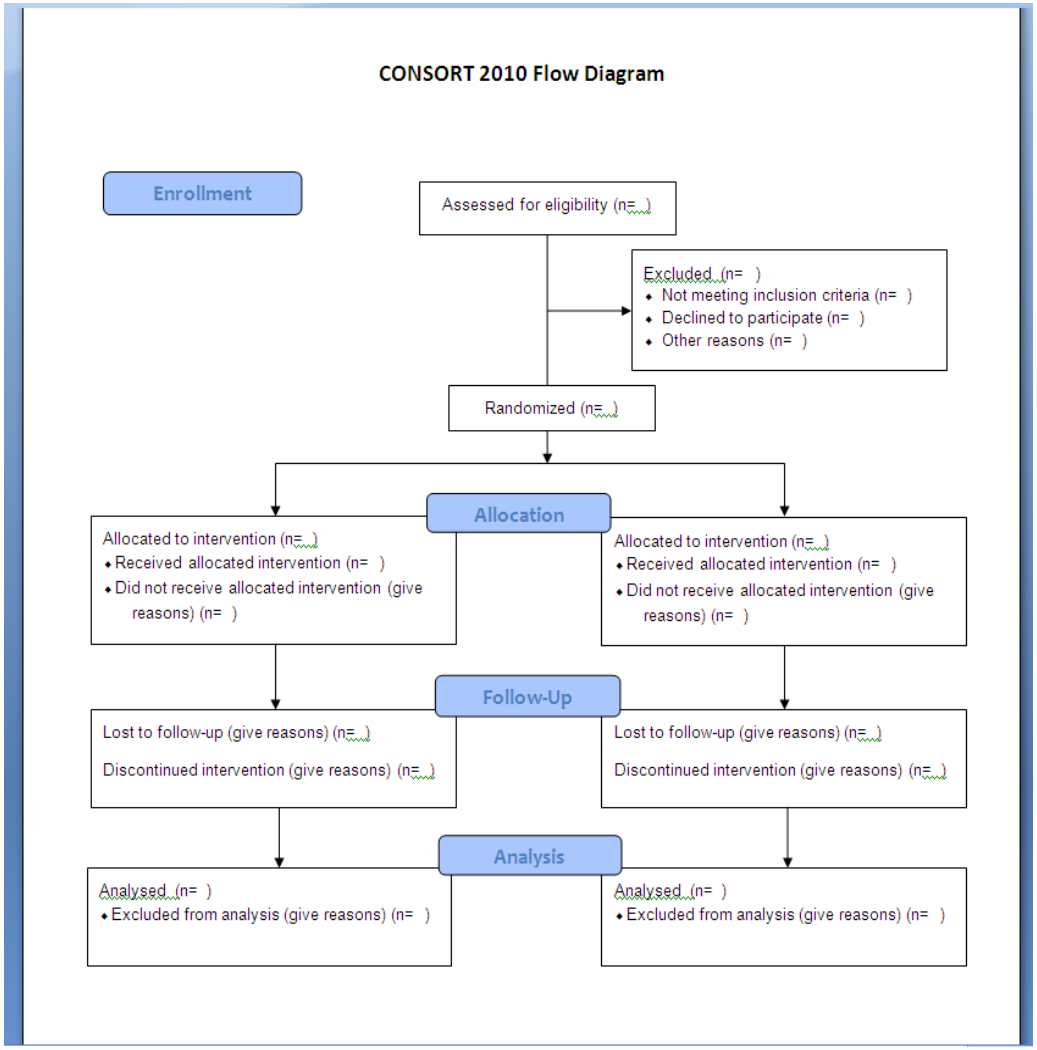
CONSORT 2010 Flow Diagram
Enrollment
Assessed for eligibility (n=)
Excluded (n=)
Not meeting inclusion criteria (n=)
Declined to participate (n=)
Other reasons (n=)
Randomized (n=)
Allocation
Allocated to intervention (n=)
Received allocated intervention (n=)
Did not receive allocated intervention (give reasons) (n=)
Allocated to intervention (n=)
Received allocated intervention (n=)
Did not receive allocated intervention (give reasons) (n=)
Follow-Up
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Analysis
Analysed (n=)
Excluded from analysis (give reasons) (n=)
Analysed (n=)
Excluded from analysis (give reasons) (n=)

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Resource Centre

- Library of health research reporting
  - Reporting Guidelines
  - Editorials introducing RGs
- Authors of research reports
- Editors and peer reviewers
- Reporting guidelines developers

Library for health research reporting

The EQUATOR Network library currently contains:

- An introduction to reporting guidelines
- Comprehensive lists of the available reporting guidelines, listed by study type:
  - Experimental studies
  - Observational studies
  - Systematic reviews
  - Qualitative research
  - Economic evaluations
  - Quality improvement studies
  - Other reporting guidelines
  - Sections of research reports
  - Specific conditions or procedures.
- A comprehensive list of guidelines, listed alphabetically by author
- Examples of editorials introducing reporting guidelines

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Thanks

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