NIH Collaboratory
Rethinking Clinical Trials®
Health Care Systems Research Collaboratory

Reporting Pragmatic Clinical Trials

Introduction

Transparent reporting of clinical trials is essential for helping researchers, clinicians, patients, and other stakeholders understand the validity and reliability of the findings. Many have suggested that the quality of trial reporting is suboptimal and have sought consensus on the key elements of transparent reporting. To address this, a group of clinical trial methodologists and journal editors developed the CONSORT (Consolidated Standards of Reporting Trials) Statement. CONSORT is intended to improve transparency and dissemination of trial findings by providing a checklist and guidance for authors.[1] The original CONSORT statement focused on the reporting of standard, two-group randomized controlled trials (RCTs) that compare an intervention with a control. Over the years, CONSORT has been expanded for clarity and revised, most recently in 2010, and now includes several official extensions to account for variations in trial design, interventions, and data (described in Appendix A).

Pragmatic Clinical Trials

The NIH Health Care Systems Research Collaboratory supports the design, execution, and dissemination of a set of Demonstration Projects, which are pragmatic clinical trials (PCTs) that address questions of major public health importance and are part of an effort to create a new infrastructure for collaborative research within healthcare systems. In contrast to RCTs, which elucidate a mechanical or biological process, PCTs are "designed for the primary purpose of informing decision makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level."[2] To be clear, PCTs are on a *continuum* with traditional RCTs, and there are aspects of PCTs that make them either more explanatory or more pragmatic (described in Appendix B). Generally, a PCT is more pragmatic if the data are collected during routine clinical care (usually through the electronic health record [EHR]); if there is some flexibility in the delivery of and adherence to the intervention; if a real-world population is included; and if the outcomes are relevant to patients and other decision makers.

Purpose of this Template

This template is intended to help authors with the transparent reporting of their PCT. While we have looked to the CONSORT guidance and extensions wherever possible, new areas are emerging related to PCTs that the CONSORT checklist and guidance do not address. These include reporting around the secondary use of EHR data, wider stakeholder and health system involvement in the conduct of PCTs, and special ethical and regulatory considerations for PCTs.

Guidance in this template is organized by the recommended reporting elements as presented in the current CONSORT checklist, and also draws on recent experiences and lessons learned from the NIH Collaboratory Demonstration Projects. We hope that the resulting report will assist authors in developing the primary journal publications. We recognize that journals have space limitations and so we encourage authors to use supplements if necessary to report all the recommended elements.

We include the following appendices:

- **Appendix A** contains a table with references to CONSORT and its extensions.
- **Appendix B** provides links to the Pragmatic–Explanatory Continuum Indicator Summary (known as PRECIS-2) tools and resources.
- **Appendix C** lists definitions of PCT-related terminology.
- **Appendix D** has examples of figures.

The Living Textbook
Extensive information and user tools are available on *Rethinking Clinical Trials®: A Living Textbook of Pragmatic Clinical Trials*, an online resource designed to provide information on how to understand, design, conduct, analyze, and disseminate PCTs. Additional resources for authors are at the end of the reference list.

_____

Title
Identify the study as a randomized, pragmatic clinical trial or, specifically, a cluster-randomized trial, as appropriate. (Optional: Convey the randomization scheme; e.g., parallel, stepped-wedge, adaptive). On the title page, include all author names, degrees, institutional affiliations and give full contact information for the corresponding author. Provide 3-5 keywords.

Abstract
Create a structured summary (background, methods, results, discussion) that includes the following information:

- Trial design (e.g., cluster, noninferiority)
- Randomization scheme (e.g., parallel, stepped-wedge, adaptive)
- Setting (e.g., hospitals, community clinics, regional healthcare system)
- Eligibility criteria for the participants or clusters
- Interventions for each group
- Whether the hypothesis pertains to the cluster level, the individual participant level, or both, and whether the primary outcome pertains to the cluster level, the individual participant level, or both
- For cluster-randomized trials (CRTs), how the clusters were allocated to interventions
- Whether participants, caregivers, and those assessing the outcomes were blinded to group assignment

- The number of participants or clusters randomized to each group and the number analyzed in each group
- Results at the individual participant or cluster level as applicable for each primary outcome
- Important adverse events or side effects
- A general interpretation of the results
- The degree of generalizability of the findings
- The trial registration name and number
- If available, where the protocol can be accessed
- The funding source and role of the funder

Introduction

Background and objectives
Describe:
- The scientific background and rationale
- The health or healthcare problem the intervention addresses
- The rationale for choosing the specific pragmatic design (includes cluster-randomized, stepped-wedge)
- Decisions the trial is intended to inform and in what setting
- Other interventions that are commonly aimed at this problem
- Key features that make the trial feasible in this setting and elsewhere
- Specific objectives, research questions, and hypotheses; for CRTs, describe whether the objectives pertain to the cluster level, individual participant level, or both

Methods

Stakeholder engagement
Because PCTs are generally conducted as part of routine care and are meant to immediately inform the delivery of care, engagement with relevant stakeholders—patients, delivery system leaders, IT personnel, clinicians, and other frontline providers—is important. Briefly describe the extent to which stakeholders were involved (e.g., defining the study question, designing the study, developing workflows, assessing feasibility).

Trial design
Describe the pragmatic aspects of the trial design: decisions related to the real-world healthcare setting, logistical considerations and clinical workflow, and service delivery. Explain the design, such as cluster randomization, stepped-wedge. Indicate if applicable whether this is a population-based study. If possible, include a schematic representation of the study design.

For CRTs, define the clusters and describe how the design features apply to the clusters. For stepped-wedge CRTs, define the timing and randomization of crossover from the control to the intervention.

Describe important changes to the methods after the trial started, and include reasons.

Participants
Frame the eligibility criteria to show the degree to which they include typical participants, providers, institutions, communities, or settings of care. Explain the method of participant recruitment and the attributes of the healthcare system or setting where the data were collected.

Intervention
Readers need a sense of how feasible the intervention would be in their setting. Give a detailed description of the intervention for each group and how it was actually administered; explain the comparator (for example, usual care) in similar detail. If the intervention included multiple components, describe each component in detail. For CRTs, indicate whether the interventions were applied at the cluster level, individual participant level, or both.

Describe any resources added to or removed from usual care to implement the intervention. Indicate whether delivery of the intervention was allowed to vary between participants, providers, or study sites. For pragmatic trials, efforts that may reduce "natural variation in the intervention and its delivery should be described. However, if reducing variation in a care process or shifting practice patterns is itself the main purpose of the intervention, this should be explicit in the title, abstract, and introduction."[3]

When relevant, include details on the experience and training (e.g., frequency, intensity) of those who delivered the intervention.

Outcomes
Explain the primary and secondary outcome measures, why they were chosen, and their relevance to participants and key decision makers. Include whether the outcomes relate to health outcomes for patients or to healthcare system improvements/efficiencies. Describe any patient-reported outcome (PRO) measures that were used to assess the intervention; include appropriate references in support of the validity and reliability of the measures used. Describe how and when the outcomes were assessed, as well as any changes to the outcomes after the trial started, with reasons. Include the length of follow-up and how it pertains to the decisions the study is designed to inform.

For CRTs, indicate whether the outcome measures apply to the cluster level, individual participant level, or both.

Sample size
Explain how sample size was determined, interim analyses, and stopping rules. If sample size was "calculated using the smallest difference considered important by the target decision maker audience (the minimally important difference), then report where this difference was obtained."[3] For CRTs, describe the number of clusters and cluster size, including whether equal or unequal cluster sizes are assumed. Indicate the intracluster correlation coefficient, as well as an indication of its uncertainty.

Human subjects protection

Describe approval by an ethics committee (e.g., an institutional review board) as well as any other oversight bodies from which approvals were obtained. If the PCT involved a regulated product, indicate whether it was conducted under IND (or its equivalent). Delineate who is considered to be a human subject in the research (e.g., patients, clinicians, others) as well as indirect subjects of the research. Include details of the type (written, oral) and mode (electronic, mail, in-person) of informed consent used, or explain if a waiver or modification of informed consent was approved and used. If so, describe what if any mechanisms were used to provide information about the research (i.e., disclosure) and if participation was specifically authorized by subjects or if and opt-out mechanism was used. If applicable, describe whether notification and/or consent was obtained before or after randomization. Describe the method of authorization used for the use of protected health information and the standards for data security. Describe the approach used for data monitoring and if applicable, the existence of a data monitoring committee. For CRTs, indicate the nature of engagement with cluster representatives (e.g., discussion, consent) and whether consent was obtained from individual cluster members.

Randomization

Sequence generation

Include the method used to generate the random allocation sequence and describe any restriction used (e.g., blocking, stratification). Describe the type of randomization (e.g., individual, cluster, nonrandomized). For CRTs, explain if stratification or matching was used.

Allocation concealment mechanism

Describe the method used to implement the random allocation sequence, including any steps to conceal the sequence until after intervention assignment. For CRTs, specify that allocation was based on clusters. Indicate whether allocation concealment was at the cluster level, individual participant level, or both.

Implementation

Explain who generated the random allocation sequence, who enrolled participants (or clusters), and who assigned participants (or clusters) to the intervention. For CRTs, describe how individual participants were included in the clusters, such as by random sampling or inclusion of all individuals identified as eligible.

Blinding

Describe whether participants, those administering the intervention, and those assessing the outcomes were blinded to group assignment. If blinding was not done or was not possible, explain why. If relevant, describe the similarity of the interventions.

"In pragmatic trials, as in the real world delivery of care, blinding of participants and clinicians may be impossible. … Authors should speculate on the effect of any suspected modifying factors, such as belief in the intervention, in the discussion [section] … Moreover, in pragmatic trials, it is still desirable and often possible to blind the assessor or obtain an objective source of data for evaluation of outcomes."[3]

Monitoring for unanticipated changes in care within study arms

As trials evolve, changes may occur in the care provided within the intervention and/or control arms that could affect the conduct or analysis of the study. For example, some components of the intervention may appear in usual care at some control sites/clusters. Contamination can be due to various reasons: unintentional spill-over of intervention effects, other healthcare initiatives that focus on the same problem, or changes in leadership, sites, or healthcare delivery system. Explain how you monitored care provided within all study arms across all sites/clusters and whether you were able to measure treatment fidelity.

Use of data from EHRs or clinical and administrative information systems

If the source of data was from a clinical or billing database instead of one created primarily for research, describe:

- The particular EHR system(s) used in the trial
- The nature of the data source and data
- The steps used in gaining permission to use the data
- How the population of interest was identified (i.e., development of phenotype definitions, use of ICD-10 codes)
  - Reference any specific standards, data elements, or controlled vocabularies used, and provide details of strategies for translating across coding systems where applicable (e.g., methods for ICD-9 to ICD-10 translation or assertion of equivalence.) If the choice of data collection or methods was informed by a data standards initiative (e.g., ACC standards), identify the relevant federal standard, standards development organization, or professional clinical or research organization that named the standard.
- Each clinical phenotype (i.e., EHR-based condition definition) used
  - Reference the location where readers can obtain the detailed definitional logic. Use of a national repository for phenotype definitions, such as PheKB or NLM VSAC, is preferred. GitHub or another repository for code is valuable as well.
- The process for linking data from different sources, including EHRs, ancillary systems, administrative and billing systems, and external sources such as CMS or regional health information exchange
- The process and results from assessment of the quality of the data. Assessment should be informed by the Collaboratory's Phenotypes, Data Standards, and Data Quality Core recommendations for data quality.
- The data management activities during the study, including a description of different data sources or processes used at different sites
- The plan for archiving or sharing the data after the study, including specific definitions for clinical phenotypes and specifications for coding system (name and version) for any coded data

Use of a clinical research network for data querying

Describe the use of a research network for querying data. This might include, for example, a [distributed research network (DRN)](), a [CTSA network](), or a [PCORnet partner network]().

Statistical methods

Describe the statistical methods used to compare groups for primary and secondary outcomes. Include methods for subgroup analyses and adjusted analyses. For CRTs, indicate how clustering was taken into account.

Results

Participant flow

Describe the flow of participants and/or clusters through the trial and include a diagram if possible (see example in Appendix D). Include the number of participants and/or clusters approached to take part, eligible, randomly assigned, receiving the assigned intervention, completing the study protocol, and analyzed for the primary outcome. Include reasons for nonparticipation of those approached to take part. Also report losses and exclusions of participants (and clusters, if applicable) after randomization, with reasons. For CRTs, the CONSORT extension for [cluster trials]() has helpful examples of participant flow diagrams.

Recruitment

List the dates of recruitment and follow-up. Explain why the trial ended or was stopped.

Baseline data

Include a table showing baseline demographic and clinical characteristics for each group (and cluster, if applicable). If appropriate, give details of [EHR-based phenotyping]() pertinent to the study.

Unanticipated changes in care within study arms

Report any unanticipated changes in care that occurred in the study arms that could affect the interpretation of the study. Describe any intervention contamination and adjustments made to the analysis to accommodate contamination.

Numbers analyzed

For each group, include the number of participants or clusters (i.e., the denominator) included in each analysis.

Outcomes and estimation

For each primary and secondary outcome, present results for each group and estimated effect size and its precision (e.g., 95% confidence interval). For binary outcomes, give both absolute and relative effect sizes. For CRTs, provide results at the individual or cluster level as applicable, and give a coefficient of intracluster correlation for each primary outcome.

Ancillary analyses

Describe results of any other analyses performed. Distinguish between prespecified and exploratory analyses.

Harms

Explain important harms or unintended effects in each group. Clarify how harms data were collected and analyzed. Describe participant withdrawals due to harms and their experiences with the allocated treatment.

Limitations

Discuss limitations of the study, addressing sources of potential bias and imprecision.

Discussion

Generalizability

Describe key aspects of the setting that determined trial results. Describe possible differences in other settings, where clinical traditions, health service organization, staffing, or resources might vary from those in your study. Keep in mind that "the usefulness of the trial report is critically dependent on how applicable the trial and its results are and how feasible the intervention would be."[3]

Interpretation

Discuss the interpretation of results, balancing benefits and harms and considering other relevant evidence. A defining component of a PCT is that it is intended to inform decision makers about benefits, burdens, and risks of an intervention. Describe the relevance to decision makers.

References

Include a full reference list with PMIDs, URLs, or DOIs.

Acknowledgments

Include names of contributors who do not qualify as authors, per ICMJE guidelines.

Figures

Potential figures (examples in Appendix D):

- Participant/cluster flow through the trial
- Stepped-wedge cluster intervention timing

Tables

Potential tables:

- Participant/cluster characteristics
- Baseline data, and if applicable, phenotype descriptions

Supplementary Materials

Authors may consider including the main URL for the trial and making available relevant toolkits, participant materials, videos, or other resources.

_____

References Cited

1. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869. PMID: 20332511. doi: 10.1136/bmj.c869.

2. Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clin Trials 2015. PMID: 26374676. doi: 10.1177/1740774515598334.

3. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008;337:a2390. PMID: 19001484. doi: 10.1136/bmj.a2390.

Additional resources for authors

- EQUATOR (Enhancing the Quality and Transparency of Health Research) Network. Library for Health Research Reporting. This website contains a comprehensive searchable database of reporting guidelines and links to other resources related to research reporting. Available at: http://www.equator-network.org/. Accessed May 3, 2016.

- Hemming K, Haines TP, Chilton PJ, et al. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ. 2015;350:h391. PMID:25662947.

- Johnson KE, Neta G, Dember LM, et al. Use of PRECIS ratings in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory. Trials 2016;17(1):32. PMID: 26772801. doi:10.1186/s13063-016-1158-y.

- Krist AH, Glenn BA, Glasgow RE, et al. Designing a valid randomized pragmatic primary care implementation trial: the my own health report (MOHR) project. Implement Sci. 2013;8:73. PMID:23799943.

Appendix A: CONSORT Guidance

The Consolidated Standards of Reporting Trials (CONSORT) encompasses various initiatives developed by the CONSORT Group to alleviate problems associated with inadequate reporting of randomized controlled trials. Their website contains user information for the 2010 update and all the current extensions. The table below has links for extensions with particular relevance to pragmatic trials.

CONSORT resources

Description	Link
CONSORT website	http://www.consort-statement.org/
CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials	Moher 2010, PubMed abstract
CONSORT checklist and explanations	http://www.consort-statement.org/checklists/view/32-consort/66-title
CONSORT extensions	
2008	Abstracts
2008	Pragmatic trials
2012	Cluster trials
2013	Patient-reported outcomes

Appendix B: PRECIS-2

The Pragmatic–Explanatory Continuum Indicator Summary tool guides trialists to prospectively consider the design of their trial across 9 domains: eligibility criteria, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis (Figure B-1). The rating scale is from 1 (more explanatory) to 5 (more pragmatic).
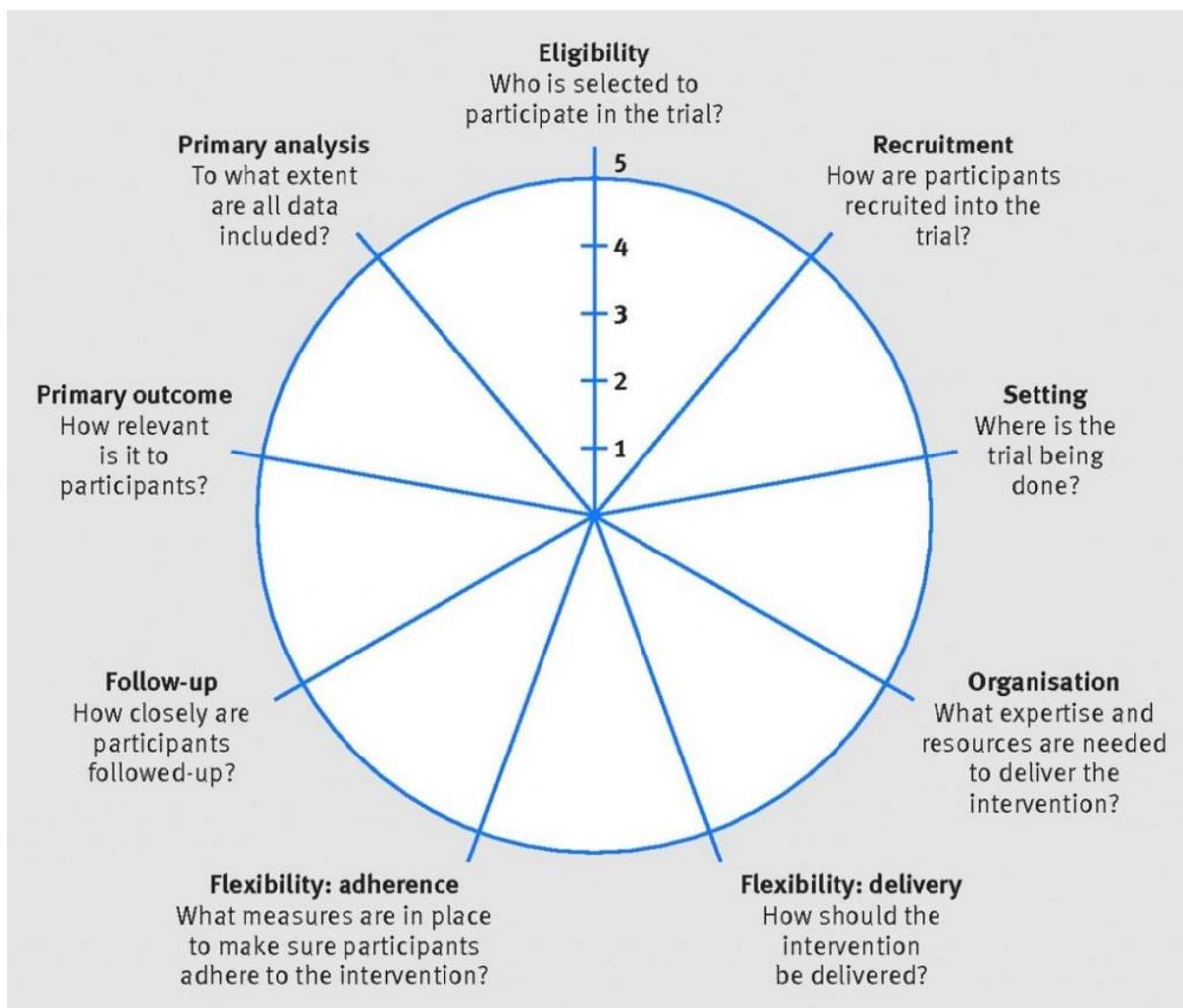
Figure B-1. PRECIS-2 Wheel

Illustration used by permission. Kirsty Loudon et al. BMJ 2015;350:bmj.h2147. Copyright 2015 by British Medical Journal Publishing Group.

PRECIS-2 resources

Description	Link
The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015;350:h2147. PMID:25956159. doi:10.1136/bmj.h2147.	Loudon 2015, PubMed abstract
Use of PRECIS ratings in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory. Trials 2016;17(1):32. PMID:26772801. doi:10.1186/s13063-016-1158-y.	Johnson 2016, PubMed abstract
An introductory YouTube video on PRECIS-2 (2:53) by coauthors Kirsty Loudon and Shaun Treweek.	PRECIS-2 video
Health Informatics Centre at the University of Dundee contains information for trialists on using PRECIS-2. The site has a database of trials spanning the pragmatic spectrum. Users can also register their trials at the website	PRECIS-2 website
An index of registered trials showing wheel ratings and other details.	PRECIS-2 wheel examples

Appendix C: Definitions

Cluster-randomized trial (CRT)

A trial characterized by random assignment of groups or clusters to study conditions and by measurement of outcomes among members of those groups or clusters. In a CRT, the cluster is the unit randomized, whereas in a traditional RCT, the individual study participant is randomized.

Computable phenotype

A clinical condition or characteristic that can be ascertained via a computerized query to an electronic health record (EHR) system or clinical data repository using a defined set of data elements and logical expressions. Queries can identify patients with a particular condition, such as diabetes, obesity, or heart failure, and can be used to support a variety of purposes for observational and interventional research. Standardized computable phenotypes can enable large-scale PCTs across multiple health systems while ensuring reliability and reproducibility.

Distributed research network (DRN)

A network infrastructure that facilitates multicenter studies using electronic clinical, administrative, and research data. A DRN provides multisite distributed querying of data resources while allowing the data to remain in the control of the data owners. It allows searchable discovery of available data resources, health systems, researchers, and reusable analytic tools. A key component of a DRN is the governance that determines how investigators and data partners interact with each another and the permissible activities within the network.

Patient-reported outcome (PRO)

An outcome reported directly by patients without interpretation by clinicians. PRO measures are often used in PCTs to assess endpoints that are meaningful to stakeholders.

Pragmatic clinical trial (PCT)

A clinical trial designed for the primary purpose of informing healthcare decision makers—patients, clinicians, administrators, policymakers, and payers—regarding the comparative balance of benefits, burdens, and risks of a health intervention at the individual or population level. PCTs are distinguished by interventions that are done in the usual care setting in a real-world population, flexibility in the delivery of and adherence to the intervention, and outcomes that are relevant to patients.

PRECIS-2

The Pragmatic–Explanatory Continuum Indicator Summary tool (revised in 2015). Few clinical trials are entirely explanatory (done in an idealized setting) or entirely pragmatic (done in a usual-care setting); rather, trials are situated somewhere along a continuum of applicability. To help trialists assess how closely their trial's design matches its intended purpose, a group of trialists and methodologists developed PRECIS, a validated design tool that guides trialists to

prospectively consider the design of their trial along 9 domains: eligibility criteria, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis.

Secondary use of electronic health record (EHR) data

The use of EHR data for research. In contrast to use of prospectively collected data, secondary use requires control over data definitions and collection in healthcare facilities, procedures for access and permission to use the data, dependence on record linkage, the need for computable definitions for cohorts and outcomes of interest, and the demonstration that data are of adequate quality to support research conclusions.

Stakeholder engagement

A process by which those who have an interest in the outcomes of trials are engaged in all phases of clinical research activities. Better stakeholder engagement has been proposed to help realign healthcare research with the needs of clinicians, patients, policymakers, and payers.

Stepped-wedge randomization

A form of cluster randomization that involves random and sequential crossover of clusters from control to intervention until all clusters are exposed to the intervention.

Appendix D: Sample Figures

Figure D-1. Example of participant flow diagram*
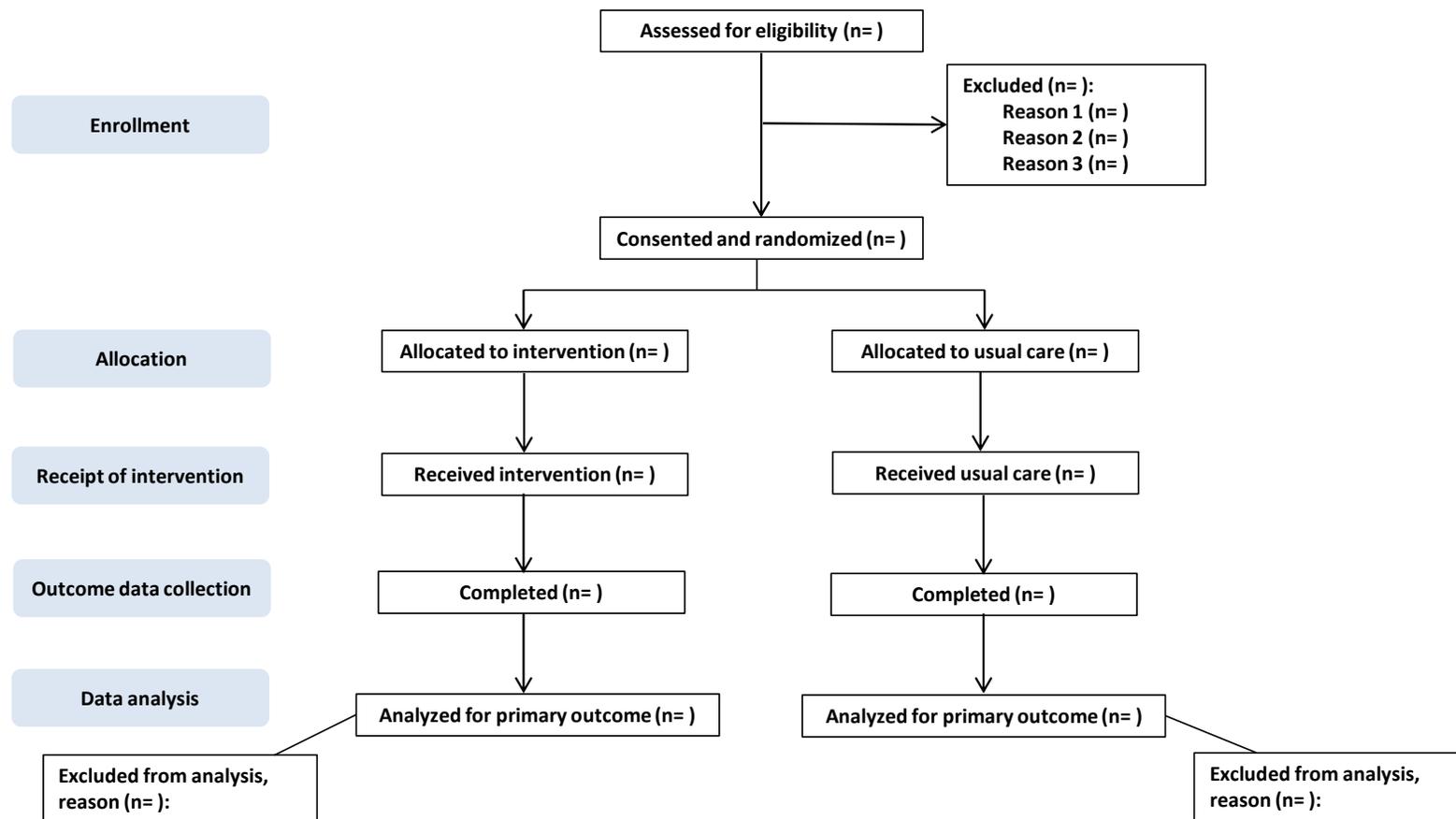
* For another example, see the STOP CRC trial's publication (Coronado GD, Vollmer WM, Petrik A, et al. Strategies and opportunities to STOP colon cancer in priority populations: pragmatic pilot study design and outcomes. BMC Cancer 2014;14:55. PMID: 24571550. doi: 10.1186/1471-2407-14-55). More examples are in the CONSORT guidance documents and extensions.

Figure D-2. Example of stepped-wedge cluster intervention timing
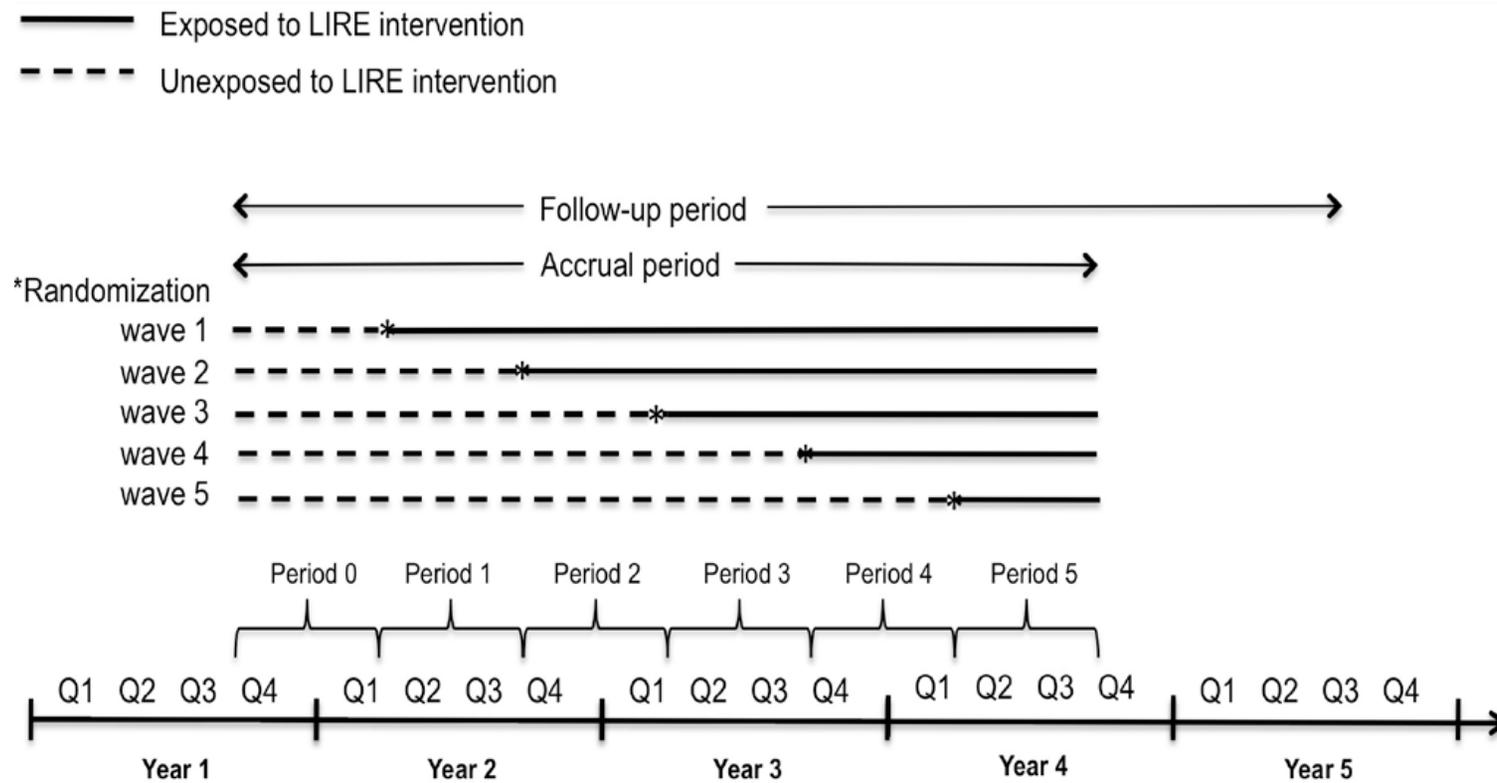
In each wave, 20 new clinics have the LIRE intervention (inserting epidemiologic benchmarks into imaging reports) until all 100 are exposed to the intervention. Figure is from NIH Collaboratory Grand Rounds slide presentation, November 6, 2015: Lumbar Imaging with Reporting of Epidemiology (LIRE): Lessons Learned. Available at: https://www.nihcollaboratory.org/Pages/GR-Slides-11-06-15.pdf. Accessed January 20, 2016.