Pre-Registration, Pre-analysis, and Transparent Reporting: *Perspectives from biomedical research*

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BITSS
Berkeley Initiative for Transparency in the Social Sciences

Outline

- History
- Registry: www.ClinicalTrials.gov
  - Is it working? What could be improved?
- Reporting Guidelines: CONSORT
  - Is it working? What could be improved?
- Extensions to observational research
- Innovations in design and analysis: combining pre-specification and flexibility

A brief history of clinical trial registration

Early 2000s:

- Patient advocacy for access to trial information (enrollment possibilities and results)
  - Ethical Principles as outlined in Belmont Report
  1. Respect for persons: protecting the autonomy of all people; Researchers must be truthful and conduct no deception;
  2. Beneficence: "Do no harm" while maximizing benefits for the research project and minimizing risks to the subjects
  3. Justice: the fair distribution of costs and
- High profile cases bring publication bias (results suppression) to the public eye
  - Selective Serotonin Reuptake Inhibitors (SSRIs) and suicide
  - Cox-2 Inhibitors (Vioxx) and Heart Attacks/Death

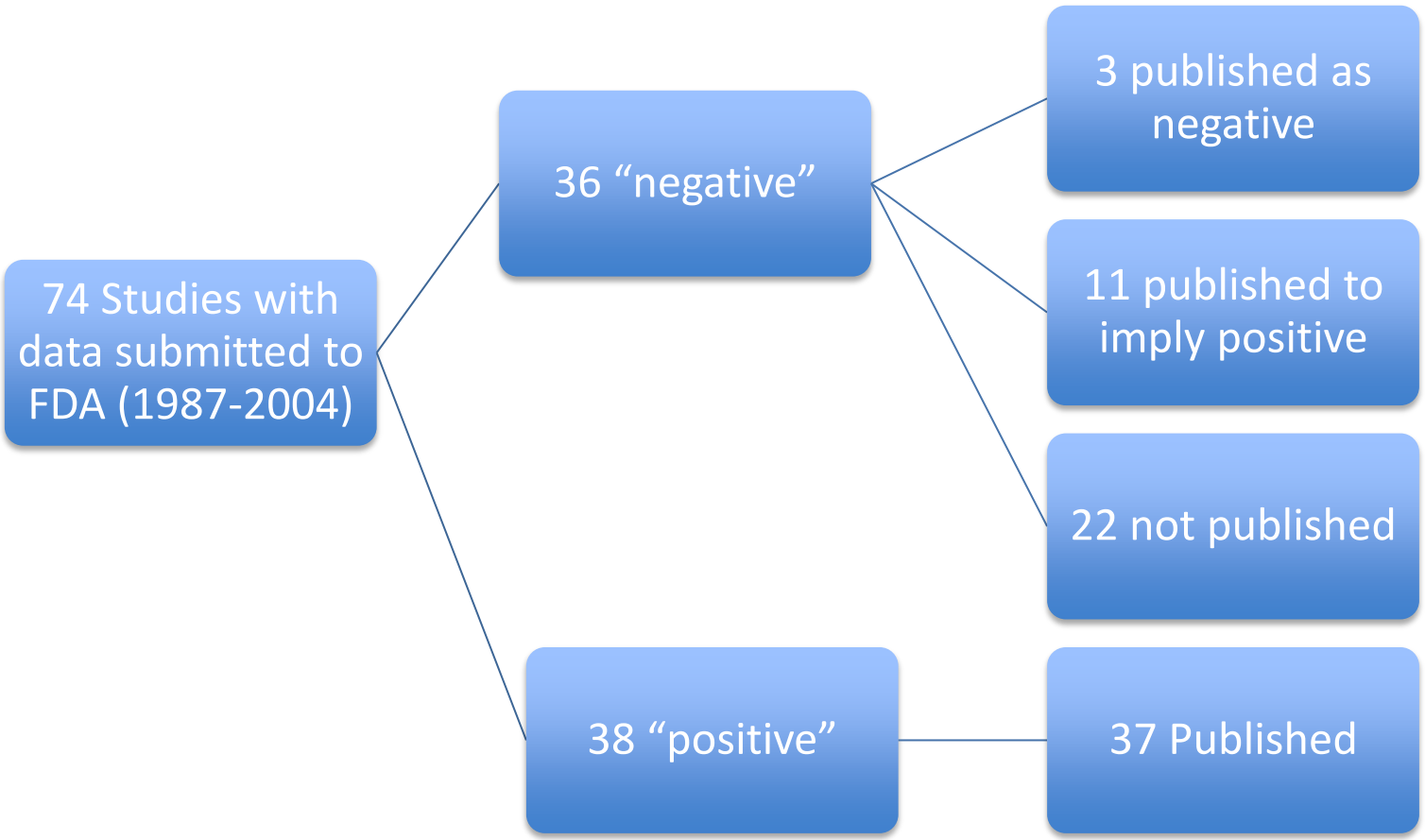
Gill CJ. *BMJ Open* 2012;**2**:e001186

High profile cases bring publication bias to the public eye

- Vioxx and heart attacks
  - Wall St Journal 2004 cites unpublished FDA study estimating >27,000 avoidable heart attacks and sudden cardiac deaths attributable to use of Vioxx.
  - Subsequent law suit and 4.85 Billion $ settlement by Merck

- SSRIs and suicide among children/adolescents
  - FDA report 2004: Increased suicide risk in children
  - "*What is disturbing about the recent report is that the purported* ***link between Paxil and suicidal thinking comes from an unpublished study sponsored by Paxil's manufacturer,*** *GlaxoSmithKline. In fact, GlaxoSmithKline has* ***published only one of its nine studies of Paxil in children and adolescents*** *to date.*" (NY Times Op Ed: Friedman 2004)

Ex. Publication Bias in Antidepressant Trials



Turner EH, et al *N Engl J Med* 2008, 358(3):252-60;
Ioannidis, *Philos Ethics Humanit Med* 2008;3:14

Push to improve objectivity in the conduct, reporting and dissemination of clinical research

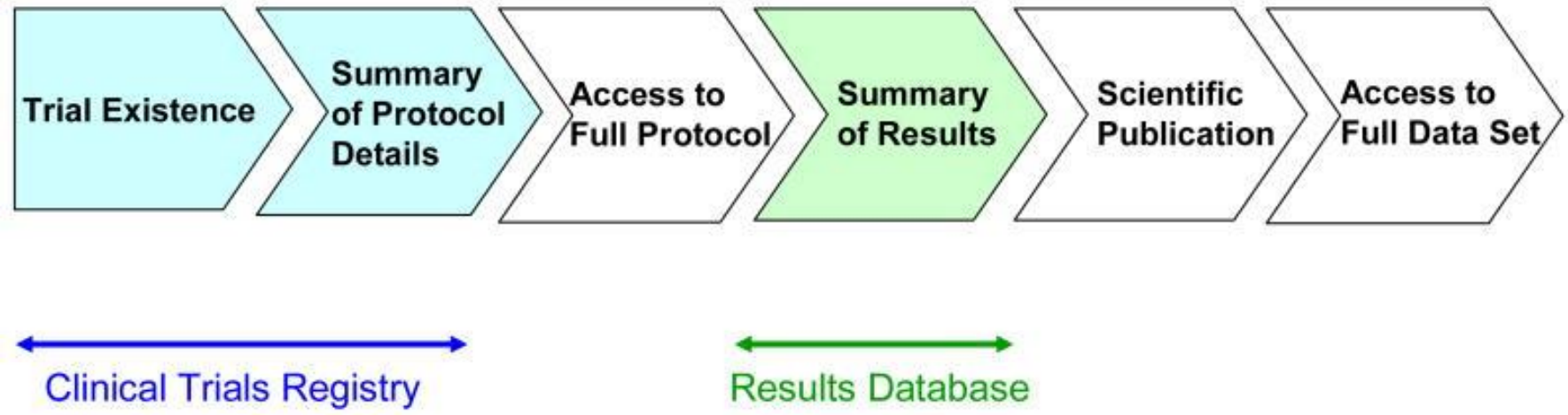
- Stricter conflict of interest standards/reporting
- Stricter requirements on financial disclosures
- Changing marketing practices by Pharma
- Open access to publications and data
- **Registration of trials and results summaries**
- **Transparent reporting**

2004: Major medical journals require trial registration as precondition for publication

"In return for the altruism and trust that make clinical research possible, the research enterprise has an obligation to conduct research ethically and to report it honestly. *Honest reporting begins with revealing the existence of all clinical studies, even those that reflect unfavorably on a research sponsor's product.*"

US Federal Law mandates registration of all clinical trials

- 1997: Registration required for selective trials
- 1999: Registry created (ClinicalTrials.gov)
- 2007: Registration/reporting requirements expanded; functionality for results upload added



Zarin, Tse; *Science*. Mar 7, 2008; 319(5868): 1340–1342.

www.ClinicalTrials.gov

- National Institutes of Health/National Library of Medicine
  - Currently: 167,286 studies; 187 Countries
- Registration of clinical trials required
  - Protocol summary prior to enrolling patients
  - Results summary within 1 year of completion
- Registration of other health studies optional
  - Observational
    - Definition: Investigators did not assign the intervention
  - Including patient registries
- Other registries also available
  - Ex: World Health Organization: www.who.int/ictrp

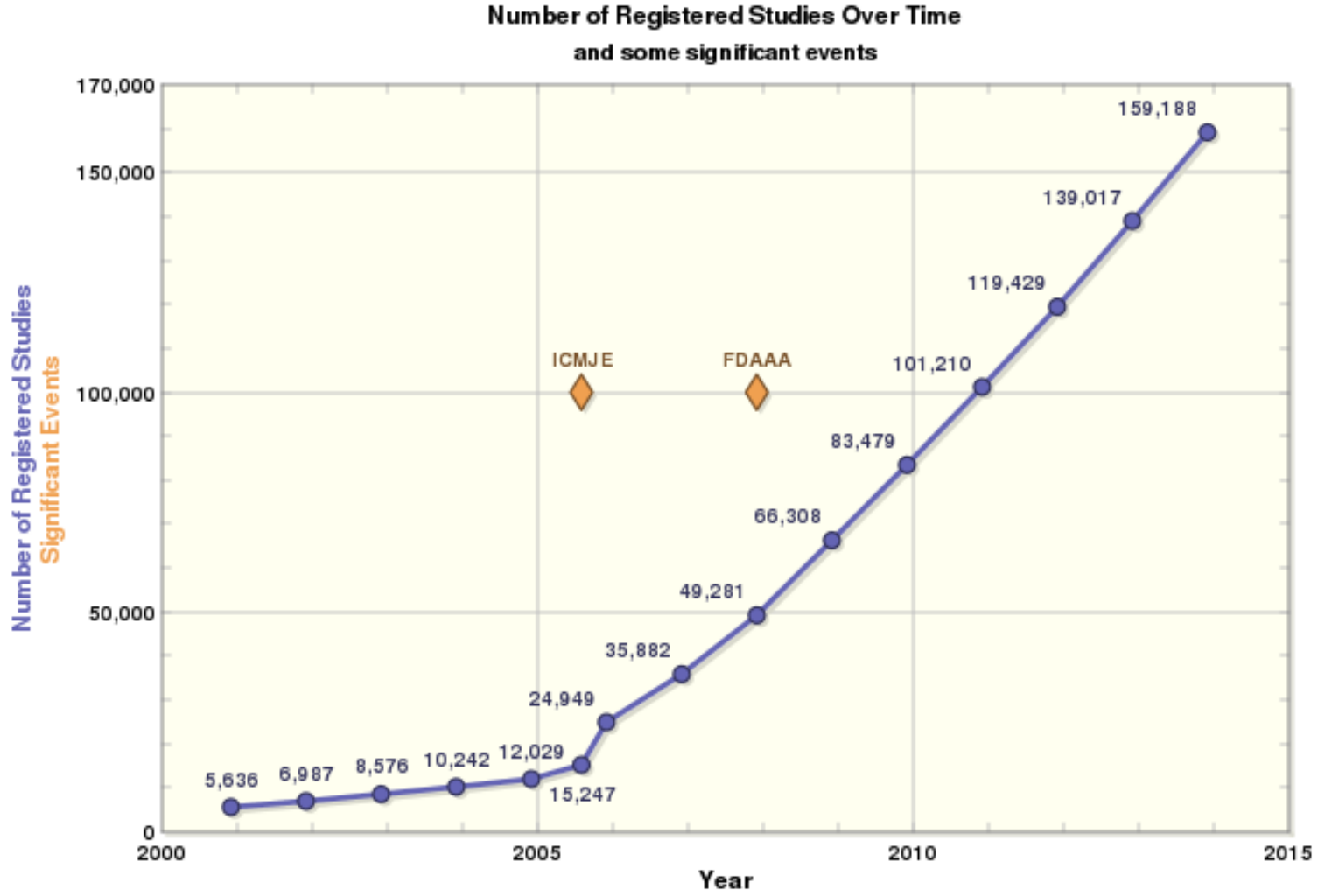
“Trial Life Cycle”: D. Zarin, NLM

1. Initial registration
2. Updates, as necessary
   - Enrollment
   - Key dates
   - Recruitment status
   - Other protocol changes
3. Initial results reporting
4. Updates, as necessary
   - **All changes tracked**

Let's look at the site…

- Ex. Ongoing study: HPTN 052
- Look at
  - Required Elements (by ICMJE, WHO also)
  - Clinical trial #- searchable: show in Pubmed…
  - Views- Tabular
  - Linked to PubMed and publications automatically
  - Outcomes and intervention, but not full analysis plan
    - Show can link to the protocol from the publication… Nov 2006
  - Look at changes- see complete history
    - Note under description- note about early stopping due to DSMB May 2011

Use of the Registry



www.clinicaltrials.gov/ct2/resources/trends

Registry provides a searchable record of unpublished studies

- <25% of registered studies published

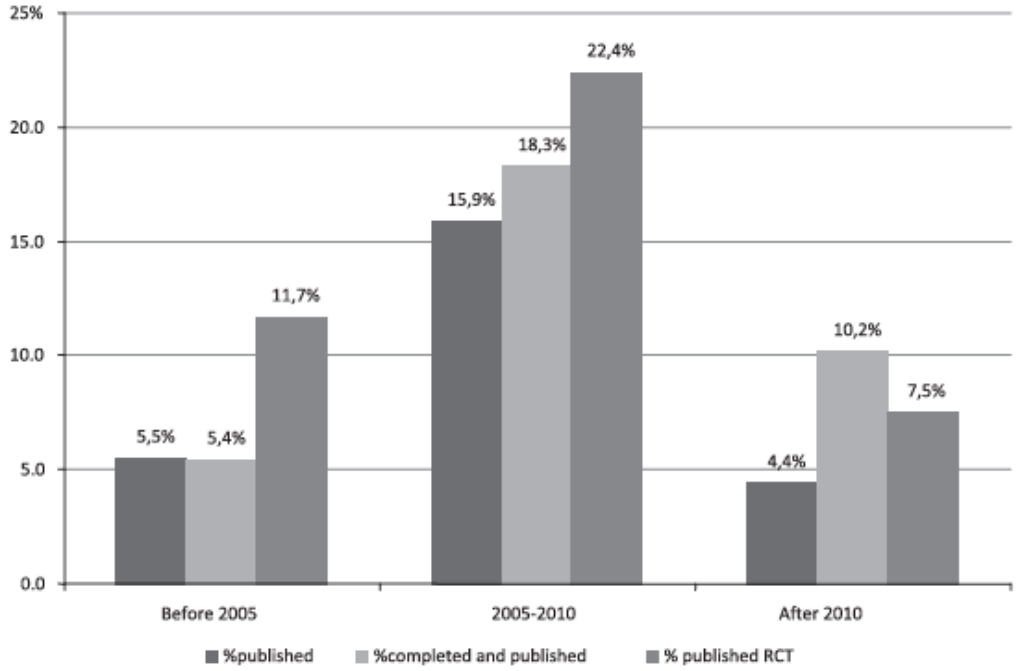


Fig. 2 Percentage of published among registered studies by the year of completion. RCT – randomized controlled clinical trials % published among all registered; % completed and published among all completed studies; % published RCTs among all registered RCTs.

Shamliyan & Kane 2014 *Journal of Epidemiology and Global Health* 4: 1-12

Imperfect Compliance

- 323 trials Indexed 2008 in high impact journals
- 45.5% adequately registered
  - Before the end of the trial
  - Primary outcome clearly specified
- Of these, 31% had discrepancies between the outcomes registered vs. published.

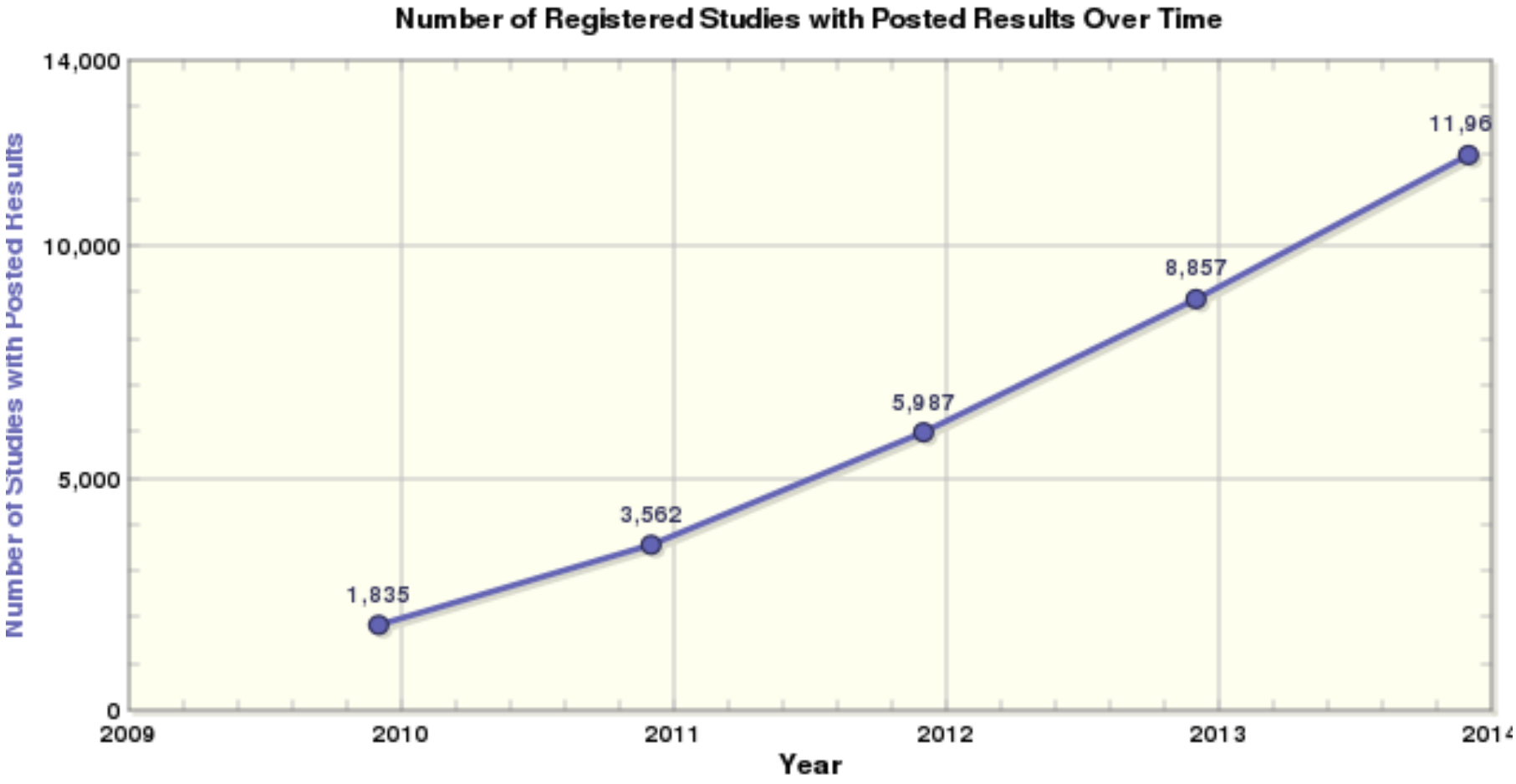
Table 2. Differences Between Primary Outcomes in Trial Registration and in Published Article for Studies With a Clear Description of the Primary Outcome in the Registry and Discrepancies Favoring Statistically Significant Results

	No. (%) of Articles		
	All (n = 147)	General Medical Journals (n = 75)	Specialty Journals (n = 72)
Articles with different primary outcomes in trial registration and in published article	46 (31.3)[a]	22 (29.3)[b]	24 (33.3)[c]
Registered primary outcome omitted in text	15 (10.2)	8 (10.7)	7 (9.7)
New primary outcome introduced in text	22 (15.0)	11 (14.7)	11 (15.3)
Different timing of assessment of primary outcome	4 (2.7)	1 (1.3)	3 (4.2)
Published primary outcome described as secondary outcome in registry	8 (5.4)	5 (6.7)	3 (4.2)
Registered primary outcome reported as secondary outcome in text	6 (4.0)	4 (5.3)	2 (2.8)
Discrepancies in primary outcome favoring statistically significant results, No.[d]	46	22	24
Yes	19 (41.3)	9 (40.9)	10 (41.7)[e]
No	4 (8.7)	1 (4.5)	3 (12.5)
Impossible to conclude	23 (50.0)	12 (45.5)	11 (45.8)

[a] Nine articles had 2 reasons for difference in primary outcome.
[b] Seven articles had 2 reasons for difference in primary outcome.
[c] Compared with general journals: $P = .73$. Two articles had 2 reasons for difference in primary outcome.
[d] A discrepancy in primary outcome was said to favor statistically significant results when a new, statistically significant primary outcome was introduced in the article or when a statistically nonsignificant primary outcome was omitted or defined as nonprimary in the published article.
[e] Compared with general journals: $P = .60$.

Mathieu et al.; *JAMA*. 2009;302(9):977-984

Results reporting on the registry



www.clinicaltrials.gov/ct2/resources/trends

Minority of Studies Report Results

- <20-25% of studies required to register results do so within 1 year of completion
- 10% of trials not-required to register results do so

Table 4 Posting of study results on Clinicaltrials.gov website indexed against number of completed trials, by year and source of study funding

Year	Source of funding			
	Industry	Non-industry	Blended‡	Total
2007*				
No. posted	73	11	4	88
No. completed in interval	260	234	74	568
% posted/completed	28.1	4.7	5.4	15.5
2008				
No. posted	434	81	53	568
No. completed in interval	1286	908	320	2514
% posted/completed	33.7	8.9	16.6	22.6
2009				
No. posted	339	86	57	482
No. completed in interval	1252	1225	406	2883
% posted/completed	27.1	7.0	14.0	16.7
2010†				
No. posted	95	31	21	147
No. completed in interval	562	696	204	1462
% posted/completed	16.9	4.5	10.3	10.1
Total				
No. posted	941	209	135	1285
No. completed in interval	3360	3063	1004	7427
% posted/completed	28.0	6.8	13.4	17.3

*Interval limited to postings from 28 September 2007.
†Interval limited to postings through 23 June 2010.
‡Industry and non-industry funding.
Analysis data set limited to US-based, intervention studies at Phase II or beyond.

Gill CJ. *BMJ Open* 2012;**2**:e001186; Prayle et al, *BMJ* 2011;344:d7373

Let's look at the site…

- Ex 1. High profile completed trial without results: HPTN 052
  - Linked to publication, supplementary materials..

- Ex. 2: Completed study with results: Healthy Love
  - Search "HIV behavioral" with results
  - Look at changes
    - Changes to primary outcomes post- date study completion
  - Look at results
  - What is and is not reported
  - Link to publication

Is results reporting useful?

- Provides an additional data source
  - Random sample 600 registered drug trials with results posted
    - Posted median 19 mo after completion (IQR 14,30)
    - 50% unpublished
    - Of those published, participant flow, efficacy and adverse events reporting more likely complete in the registry
  - Meta-analyses/systematic reviews increasingly searching registry
  - Only 34% of reviewers consult the registry
- "*The usefulness of ClinicalTrials.gov ultimately depends on whether responsible investigators and sponsors make diligent efforts to submit complete, timely, accurate, and informative data about their studies*" (Zarin 2011 NEJM)

Riveros PLoS Med 2013; Mathieu PLoS One 2013

ClinicalTrials.gov: Lessons Learned

- Journals can have a transformative impact
- Low compliance with results registration, even when required by Federal Law
- Registration does not prevent
  - Publication bias
  - Lack of transparency in analysis, reporting trial results
  - Selective outcome reporting
- Registry does provide a valuable record
- Translating this into greater accountability?
  - Growing literature based on analyzing the registry
  - Changing norms

Transparent Reporting Initiatives

- CONSORT: Consolidated Standards of Reporting Trials
  - www.consort-statement.org
- Objective: "Create Unified Standards to improve the quality and transparency in reporting of clinical trials"
  - Development led by medical journal editors, clinical trialists, epidemiologists, and methodologists
  - 1996; updated 2010
- 25 Item Checklist
  - Reporting how the trial was designed, analyzed, and interpreted
- Flow Diagram
  - Progress of all participants through the trial
- Required or endorsed by many journals

CONSORT Checklist (1)

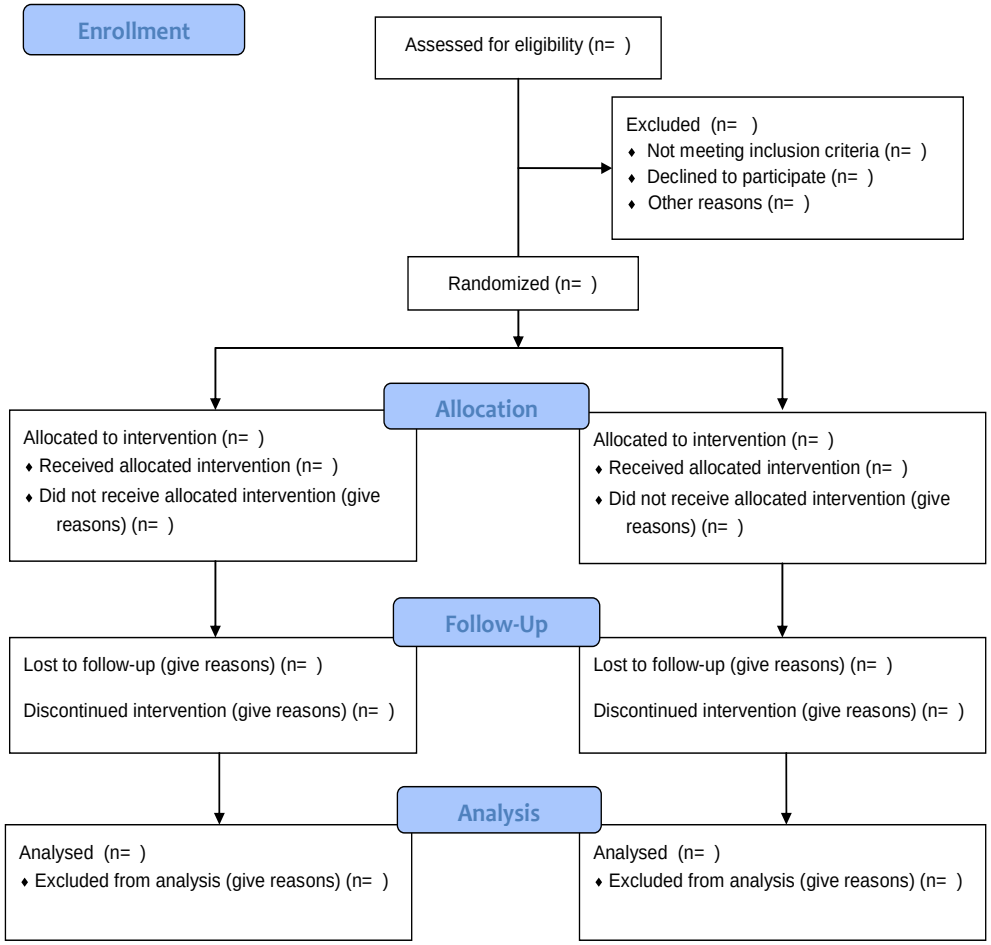
Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	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	

CONSORT Checklist (2)

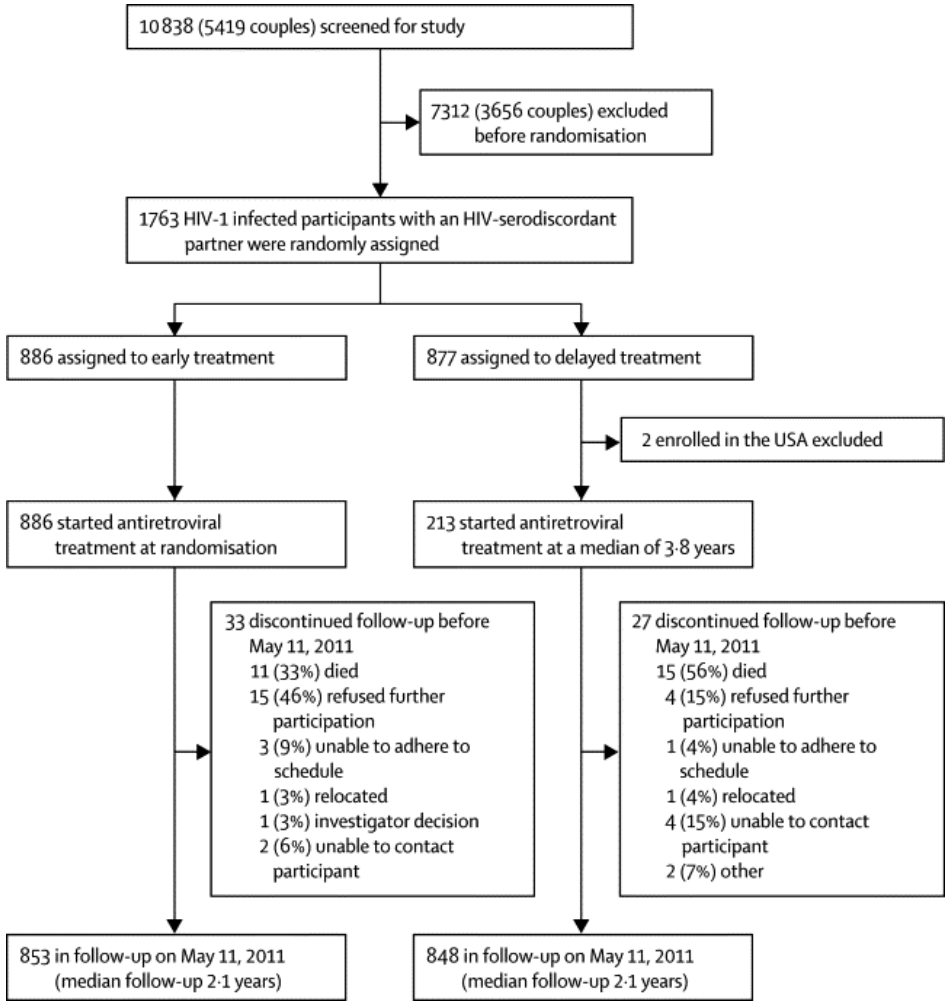
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants 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.

CONSORT Flow Diagram



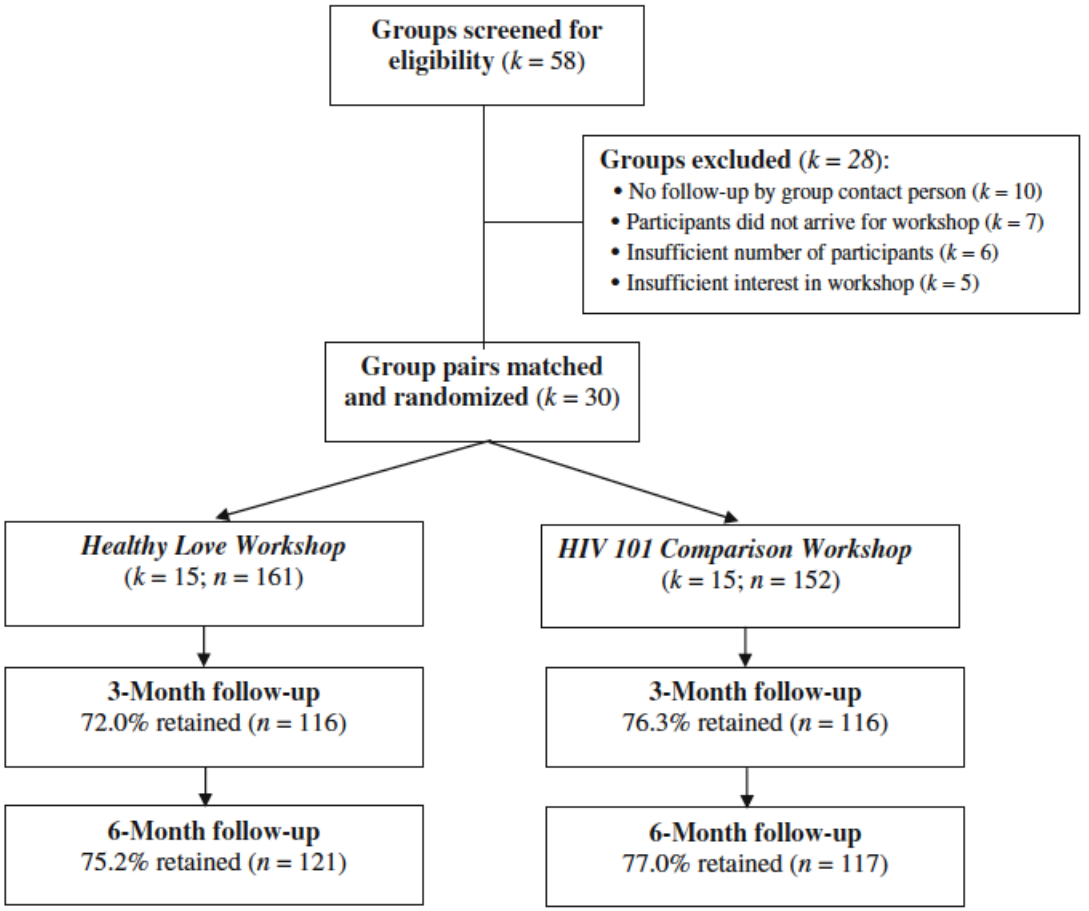
Example 1: HPTN 052



Grinsztejn et al, *The Lancet Infectious Diseases*, 14 (4), 2014, 281 - 290

Example 2: "Healthy Love"

Fig. 1 Flow diagram of participant recruitment, allocation and retention in an evaluation of the Healthy Love Workshop, Atlanta, Georgia, 2006–2007 (*Note*: *k* refers to number of groups; *n* refers to number of women)



Diallo et al, *AIDS Behav* (2010) 14:518–529

CONSORT Lessons Learned

- Highly cited; high profile
- Change practice? Probably some
  - Meta-analysis of studies looking at compliance with CONSORT
  - Post- CONSORT and endorsing journals have more complete reporting by some measures
    - Adverse events, participants analyzed, baseline data
- Compliance is imperfect even among endorsing journals
  - Variability in how endorsing journals apply/enforce guidelines
- Guidelines for reporting analyses are vague
  - Ex: # 18: "Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory"

Turner et al, *Systematic Reviews* 2012 1:60

A limitation of both…

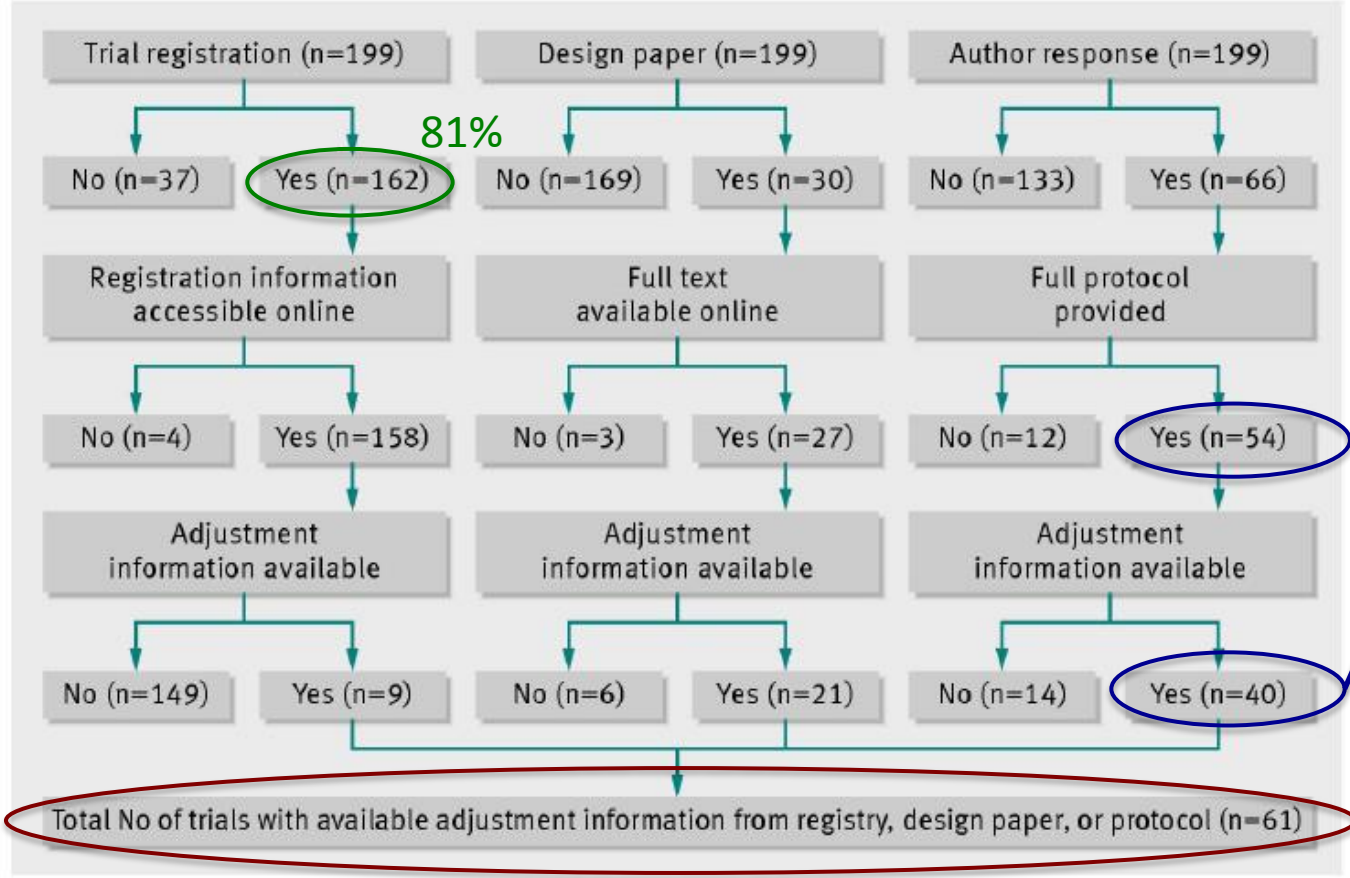
- Much of the clinical trial transparency framework works best for unadjusted comparisons of outcomes between randomization groups….
  - Easy to pre-specify and harder to manipulate
  - But limiting, and does not reflect practice
    - 50% of a random sample of trials reported adjusted results for primary outcome (Saquib et al, BMJ 2013)
- More complex methods needed (and often used) to
  - Improve power
  - Reduce bias due to loss to follow up/missing data
  - Answer more complex questions
    - As treated effects, effects among compliers, mediation effects, spill over…
- Neither the registry nor reporting guidelines capture the many analytic decisions that go into these analyses

Analysis Plans in Practice: Ex HPTN 052

- Registry: Primary and secondary outcome specification
- Data Protocol
  - Hyperlinked from primary publication
    - *This is not the norm
  - Dated
  - See TOC
  - More detail, but still a lot left unspecified
    - P. 99
- Fully specified Analysis Plan
  - Likely on file
  - Not (to my knowledge) registered

Full analysis plans are rarely pre-specified

- 200 trials published 2009 in highest impact journals



27% provided full protocols on request

74% of those protocols pre-specified adjustment plan

31% overall pre-specified adjustment

- **Of those that did, analysis plan and publication differed in 47%**

Saquib et al, *BMJ* 2013;347:f4313

A tough problem…

- On the one hand…without pre-specification -> bias and misleading inference
  - "protocols need to be entirely transparent and their analysis plans explicit in detail upfront. There should be no room for flexibility in the collected data and performed analyses." Ioannidis, *Philos Ethics Humanit Med* 2008
- On the other hand…Optimal analysis often requires flexibility
- Examples of both from Social Sciences coming up next… (Kate Casey)

Observational data are even more challenging

- Even with a pre-specified hypothesis, observational analyses often entail many more analytic decisions
  - Identification strategy
    - Difference in difference, adjustment for measured confounders, IV, etc
  - Estimator
    - Outcome regression methods, propensity score matching/adjustment/reweighting, etc.
  - Model specification
    - Which adjustment variables to include in outcome regression, functional form, etc..
- And what about exploratory analyses, hypothesis generation, unexpected findings…?
- Both registration and pre-specification challenging- and arguably more important than ever…

Where are we with observational studies? Registration

- Available (Ex. www.clinicalTrials.gov)
- Not required by major journals
- Rarely done
  - 90+% of studies published each year are observational
  - 18% of studies registered at ClinicalTrials.gov are observational
    - N=31,449
  - Those registered largely secondary analyses of registered trials, or have purely descriptive aims
- Registered pre-analysis plans rare
  - Some information often available in "concept sheets" that must be approved prior to some database release

Dal Re ScienceTranslationalMedicine.org, 6(224):1-4. 2014;
www.clinicaltrials.gov/ct2/resources/trends

Where are we with observational studies? Transparent Reporting

- Standardized Reporting Guidelines
  - Ex. Strengthening Reporting of Observational Studies in Epidemiology (STROBE)
  - www.strobe-statement.org
- Journal endorsement still not the norm (but growing)
- Distinct checklists for various study designs
  - Example: Cohort checklist

Strobe Checklist for cohort studies (1)

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses

Strobe Checklist (2)

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		

Where are we with observational studies? Transparent Reporting

- Transparency declaration: BMJ 2013
  - "The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

- Given the complexity of many observational analyses, what does this mean in practice?

Altman DG, Moher D. BMJ 2013: 347

Should we register observational studies?

THE LANCET www.thelancet.com Vol 375 January 30, 2010

Should protocols for observational research be registered?

The Registration of Observational Studies—When Metaphors Go Bad

The Editors

Epidemiology • Volume 21, Number 5, September 2010 www.epidem.com | 607

Making Prospective Registration of Observational Research a Reality

Rafael Dal-Ré,[1*†#] John P. Ioannidis,[2*†] Michael B. Bracken,[3*†] Patricia A. Buffler,[4] An-Wen Chan,[5] Eduardo L. Franco,[6] Carlo La Vecchia,[7] Elisabete Weiderpass[8]

www.ScienceTranslationalMedicine.org 19 February 2014 Vol 6 Issue 224 224cm1

The Debate: Be careful!

- Growing discomfort with how often we get things wrong
- Need to maintain our foundation for valid statistical inference

Should we register/pre-specify observational studies? **Yes**

- Same rationale as randomized trials
  - Ethics
  - Knowledge dissemination/avoidance of unnecessary duplication
  - Guard against publication bias
  - Ideally detailed analysis plans would also be registered
- Little burden
  - Observational studies need IRB approval
  - Register the protocol
- Can incorporate flexibility
  - Register changes to protocol
  - Delineate between pre-specified and post-hoc hypotheses

Dal Re et al, *Science and Translational Medicine*, 6(224):1-4. 2014

The Debate: Use data fully!

- Increasing access to huge rich data sets, increasingly available in real time= opportunity
  - Lots of subjects, lots of variables, lots of "complexity"
- Optimizing impact means finding ways to accelerate, not slow, the cycle of learning from data

Should we register/pre-specify observational studies? **No**

- We will test many fewer hypotheses
  - Reduce new and unexpected findings
- We may test them less rigorously
  - Pre-specified analyses may give us less valid hypothesis tests
  - "Protocol adaptations can improve recruitment, allow more accurate measurement of study variables, implement alternative analyses to control confounding, and incorporate new knowledge published by others." (Lash, Epidemiology 2010)
- We will learn more slowly
  - The drug approval process is notoriously slow
  - "cancerous growth of bureaucracies to protect human subjects in observational studies"(Editors, Epidemiology 2010)
- Simply allowing for post-hoc analyses designated as such is not sufficient
  - If analyses not pre-registered and fully pre-specified are penalized in the review and publication process

Towards an adaptive learning paradigm…

- Accelerating the cycle of learning from and responding to data
  - Optimize flexibility in a pre-specified way-> maintain statistical rigor

1. **Flexibility in design**

- Sequentially Randomized Trials to evaluate adaptive interventions
  - Interventions that assign or alter an individual's treatment over time based on the evolving characteristics (such as response) of that individual
- Adaptive Trial Designs:
  - Change your trial design (eg. primary hypothesis) based on looking at the data
  - Modify what types of subjects you enroll, what arms you randomize them to…

2. **Flexibility in analysis**

- Targeted Learning
  - Combine machine-learning and statistical inference
  - Look at the data to decide which variables to adjust for, model specification
- Data-adaptive parameters
  - Choose your estimand based on looking at the data

Ex.1: Sequentially Randomized Trials

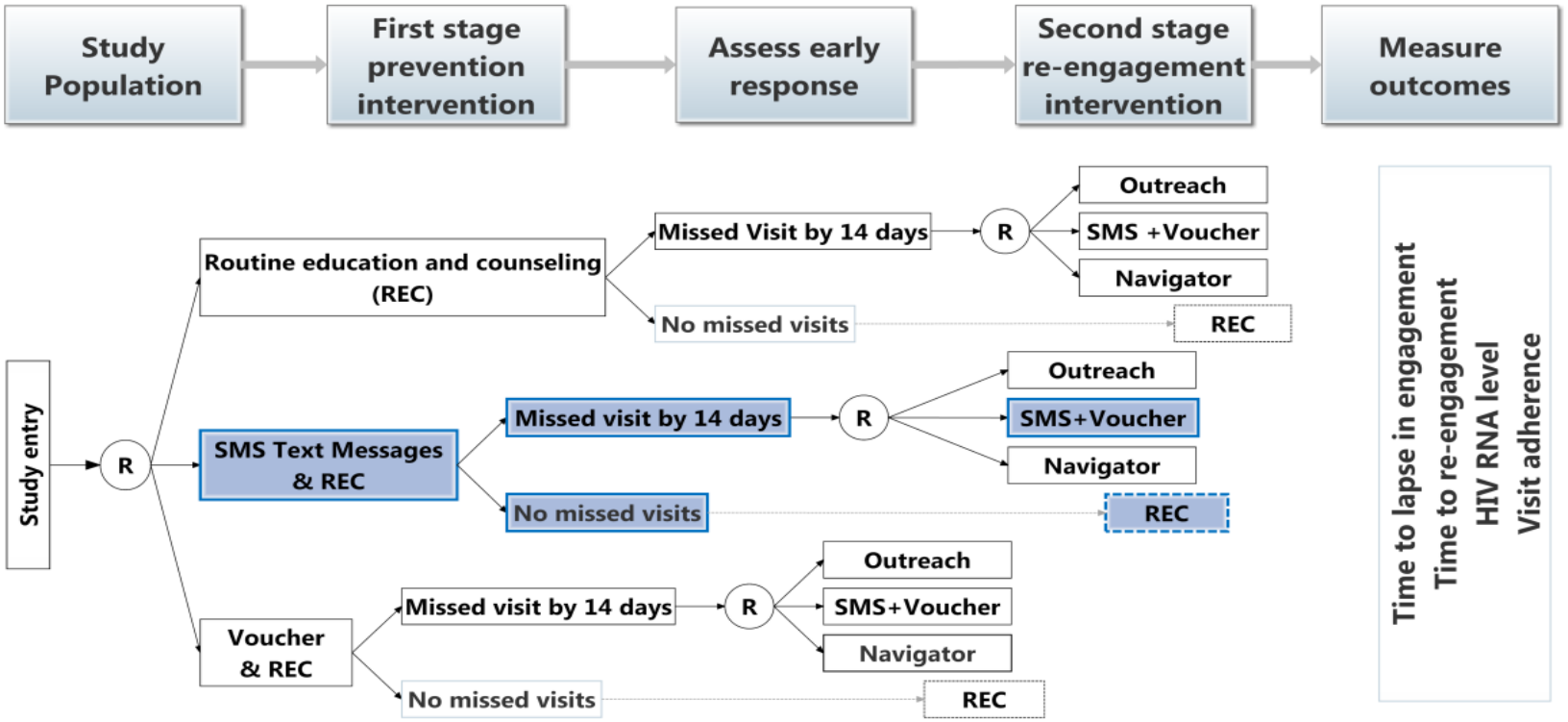
- Also called Sequential Multiple Assignment Randomized Trials (SMART)
- Evaluation of "Adaptive strategies": Strategies for assigning intervention over time based on evolving individual characteristics
- Design

1. Subjects randomized to a 1st line intervention
2. At pre-specified decision points, randomized to a 2nd line intervention,

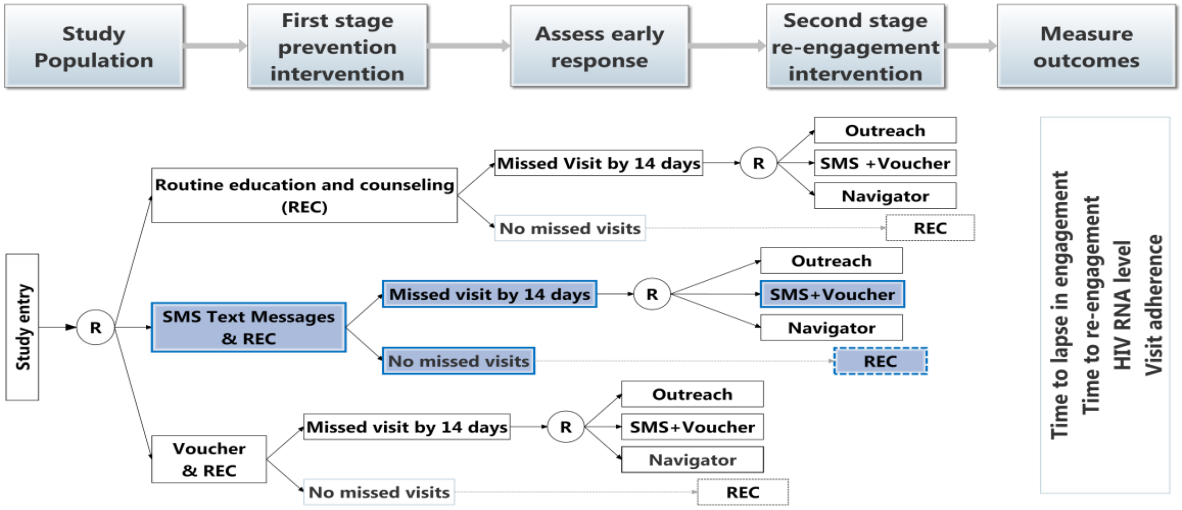
- Set of arms randomized to at each stage can depend on the past

"An Adaptive Strategy for Preventing and Treating Lapses of Retention in HIV Care (AdaPT-R).

- 2500 Adult HIV patients in Kenya
- Best (most effective and cost effective) strategy to keep them engaged in care?



SMART: Evaluate and compare wide range of adaptive strategies



- "Embedded strategies"
  - Ex: 1st line: SMS for all patients; 2nd line: SMS + Voucher for those that fail 1st line
- Strategies with a greater degree of personalization ("tailoring")
  - 1st line: Voucher for patients who live "far" from clinic, SMS for the rest
  - 2nd line: Peer Navigators for those that fail 1st line and report "low" satisfaction with care, SMS + Voucher for those who fail 1st line and report "high" satisfaction
  - Can estimate how best to define "far" and "low" without sacrificing inference

Ex. 2: Targeted Learning

- General Statistical methodology
- Address conundrum:
  - Pre-specified parametric models misspecified-> bias
  - Data too high dimensional for simple non parametric approaches
  - Machine learning methods alone- not targeted at the right thing and no good way to get inference (p-values, confidence intervals)
- TMLE: Combines state-of-the art machine learning and robust statistical inference
- Efficient (minimal asymptotic variance)
  - If nuisance parameters estimated consistently
- Often nice robustness properties

Targeted Learning, van der Laan & Rose, 2011;

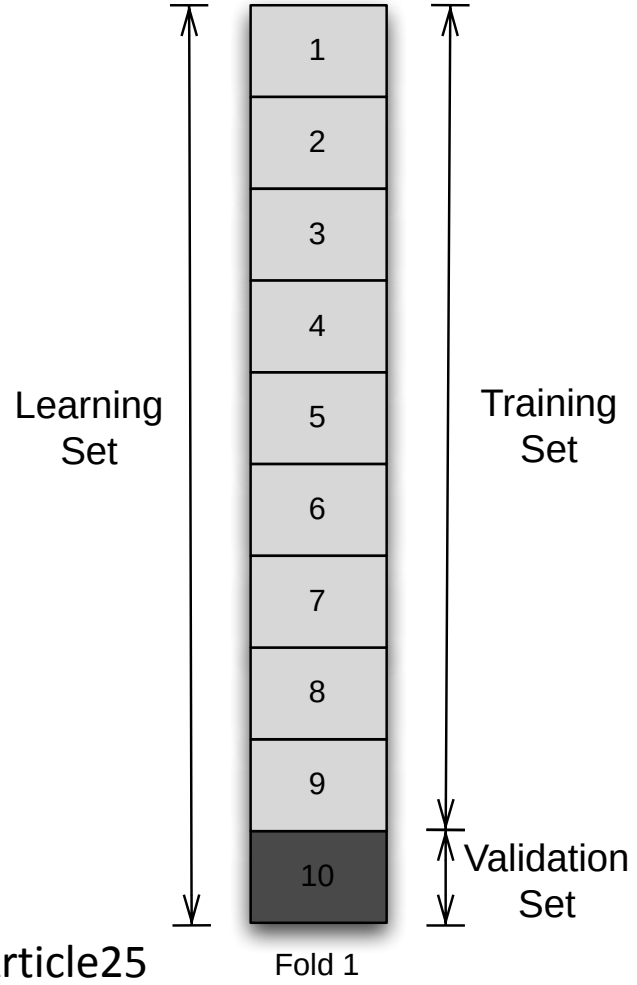
Targeted Maximum Likelihood Estimation

- For Average Treatment Effect
  - Of a point treatment A on outcome Y
  - Using observational data- confounding by baseline covariates W
  - Estimand: $E_W[E(Y|A=1,W)-E(Y|A=0,W)]$
    - Adjust for measured baseline covariates

1. Estimate outcome regression: E(Y|A,W)
   - Use a machine-learning algorithm
     - Ex: Super Learner
   - Consistent, but wrong-bias variance tradeoff for estimand, and no good inference
2. Update this fit in a targeted way
   - Reduce bias for estimand
   - Regain statistical properties for reliable inference

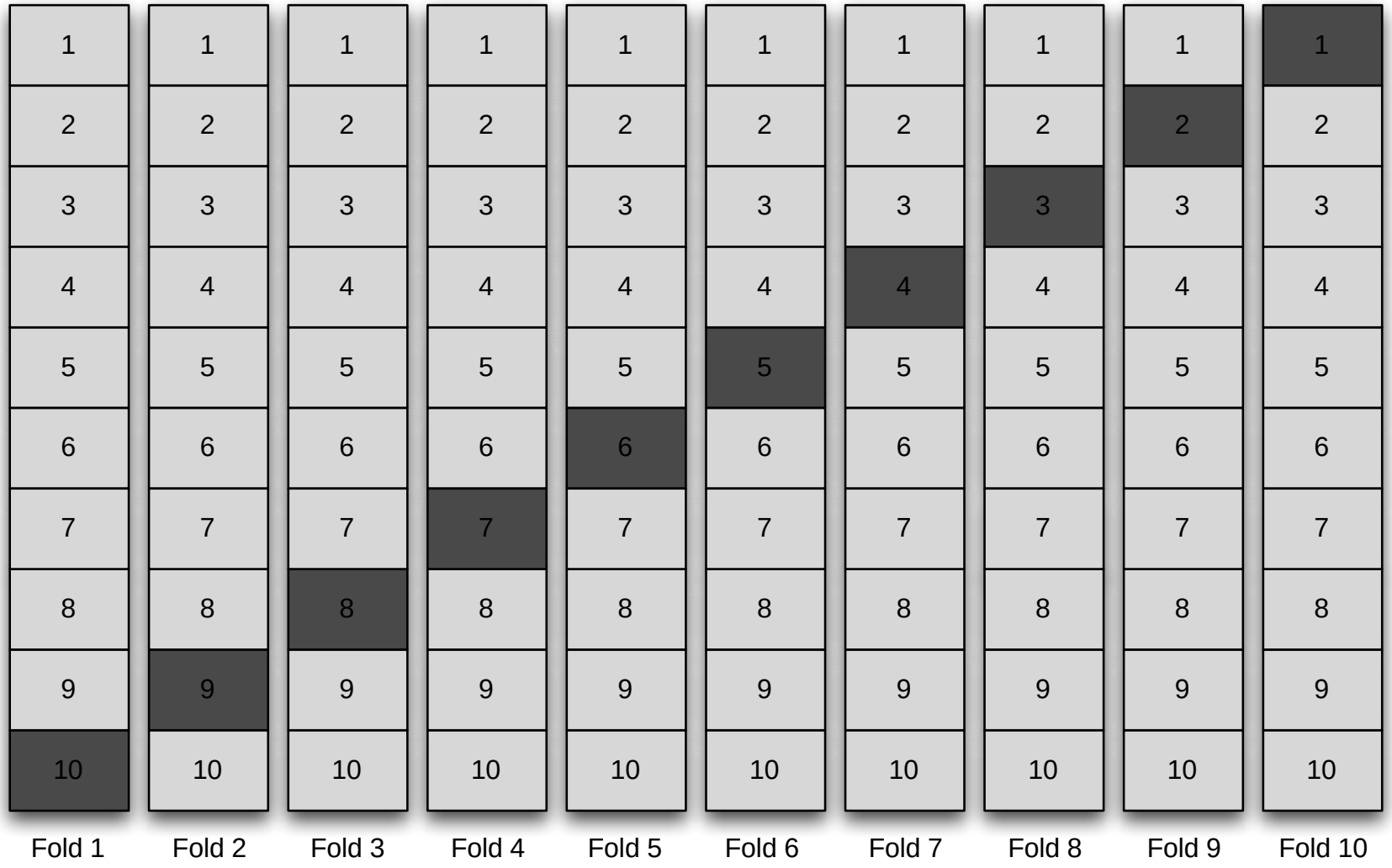
Super Learner

- User inputs a library of algorithms
  - eg Lasso, Classification regression trees, a large set of parametric regression models with different specifications
- Cross validation to choose the "best" algorithm
  - User-specified loss function
    - Ex. –log, squared error
  - More accurately, the best convex combination of algorithms



van der Laan et al, Stat Appl Genet Mol Biol. 2007;6:Article25

V-fold Cross Validation



Conclusion

- Biomedical research grappling with this issue for a while
  - Some good progress
    - Awareness/Culture change
    - Registration systems in place and being used (even if imperfectly)
    - Move towards more transparent reporting
  - And a long way to go
    - Registered fully pre-specified analysis plans remain rare
    - Continued debate on whether and how to extent to observational studies
- Convergence between the biomedical and social sciences
  - Subject matter: Health behaviors, health and development, …
  - Methodology: Big Data, Transparency, Replication…
- Biomedicine can learn a lot from the transparency movement in the social sciences…

Ex: TMLE vs. in Genomixcs Example

- Quantitative Trait Loci mapping in Listeria (Wang et al)

Table 23.3 The estimates of effect sizes and positions of QTL genes from CIM and TMLE in Listeria data set. QTL genes with FDR-adjusted *p*-values smaller than 0.05 are reported

		CIM			C-TMLE		
QTL ID	Type	Chr	cM	Effect size	Chr	cM	Effect size
1	dom	1	15.0	−0.2351	–	–	–
2	dom	1	72.8	0.1606	–	–	–
3	add	1	78.8	−0.1349	1	78.1	−0.1074
4	dom	2	14.0	−0.2623	–	–	–
5	add	2	18.0	−0.1744	–	–	–
6	dom	5	0.0	−0.1468	–	–	–
7	dom	5	61.0	−0.1693	–	–	–
8	add	5	18.1	0.2764	5	26.1	0.1960
9	dom	6	33.8	−0.1235	–	–	–
10	dom	12	41.8	−0.2352	12	40.1	−0.1372
11	add	13	22.7	−0.3409	13	14.4	−0.1668
12	dom	13	25.9	0.3525	13	26.4	0.1458
13	add	15	25.1	0.1540	15	22.1	0.0678
14	dom	15	12.0	0.2042	15	22.1	0.1438
15	add	18	–	–	18	14.1	−0.0692

Ch. 23; Targeted Learning, van der Laan & Rose, 2011;