How Journals Use CONSORT: Experiences at PLoS

EQUATOR Reporting your RCT 2010

Emma Veitch, Senior Editor, *PLoS Medicine*

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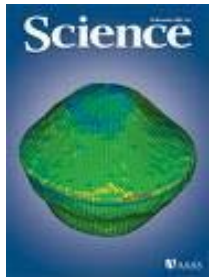
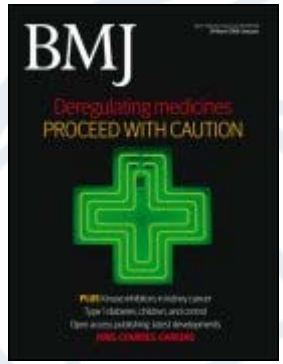
There are many different types of journals out there – and as many different peer review systems





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Why are journals important in moving towards better reporting?

- Once, journals were (pretty much) the only mechanism for publishing results of trials and other studies
- Now - increasing focus on web registries – eg clinicaltrials.gov, company websites
- But journals still provide the main method of disseminating full details of trial design and results
- Investigators still want peer-reviewed journal publication as credit for what has been done
- Peer review and editorial process provides an important opportunity for achieving good quality reporting

The life cycle of a research article

Research

Submission

Rejects

Peer review

Publication

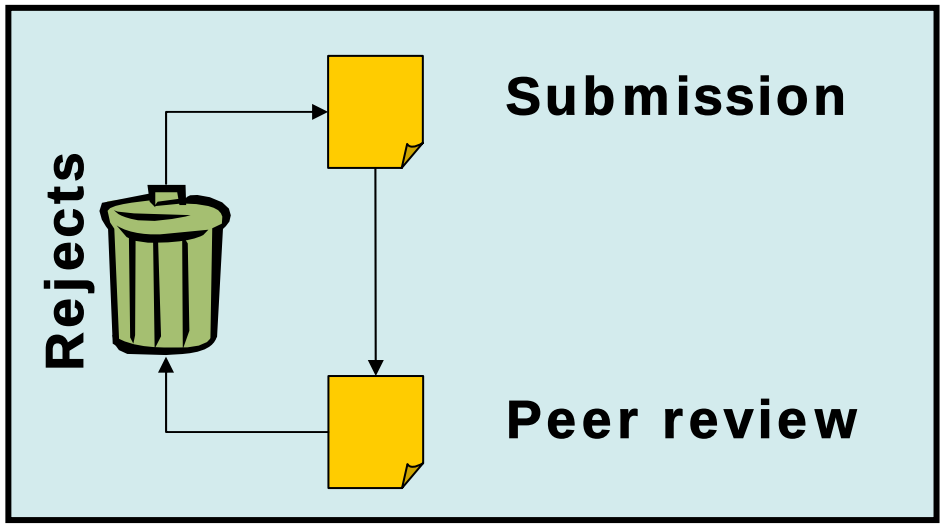
2-3 Experts

Is it rigorous?
Good enough?
Right audience?

Takes months/years

Journal name is key

What goes on in the black box called “peer review”?



At *PLoS Medicine*:

- Papers handled by in-house editor
- Additional advice from external academic editor (researcher / clinician)
- Around 90% papers rejected *before* peer review based on scope, quality, importance
- Typically 2-3 subject reviewers (eg in the clinical specialty)
- 1 statistical reviewer
- Around 50% papers rejected *after* peer review – eg prove not to be methodologically robust

How *PLoS Medicine* uses CONSORT during the editorial process

- RCT submissions **must** include CONSORT flowchart and checklist to get through to editorial assessment
- These items also made available to academic editor, peer reviewers (including statistician)
- We encourage authors reporting non-randomized trials (eg single-arm) to use applicable parts of CONSORT guidance
- Editors and peer reviewers consider how well specific items in CONSORT have been reported
- Editors give further guidance / advice to authors on improving writeup if a revision is invited

PLoS journals – additional standards for trials reporting

ICTRP International Clinical Trials Registry Platform

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- Trial registration: require prospective registration in WHO ICTRP approved registry
- Authors must also provide a copy of the original trial protocol
- Editors and peer reviewers check protocol, registry record, for key items
- Encourage authors to be more upfront in describing changes from protocol in their paper

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What do editors look for in research papers?

- Does the study ask an important question?
- Is the design appropriate, and sufficiently robust, to answer that question?
- Are the findings relevant to practice or policy?
- If YES, YES, YES – consider further
- Even if the outcomes are “negative” or “disappointing”!

Caution: ways in which journals can introduce bias

- Journals want to publish new and interesting papers
- May be a tendency for editors / reviewers to suggest emphasis on the “positive” parts of a study, shift focus away from disappointing outcomes
- This can give rise to outcome reporting bias
- Lack of space may mean some editors can’t include fully detailed methods – eg protocol deviations etc
- Lack of time may mean editors can’t always help authors use CONSORT to apply it to their study

Specific examples – applying CONSORT guidance to real papers

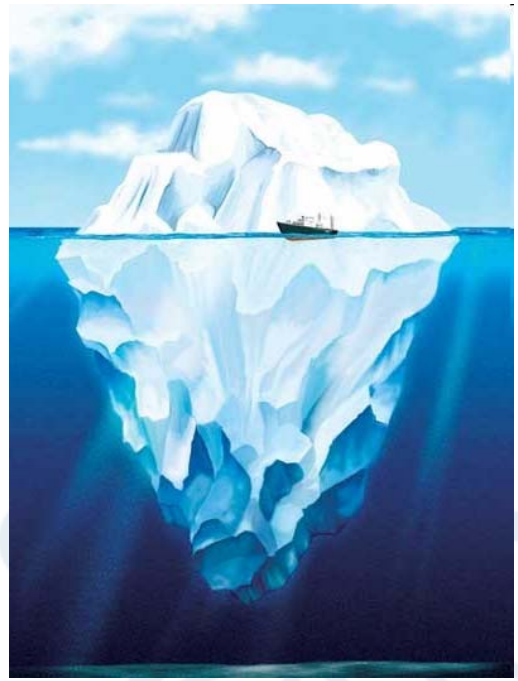
- Many researchers think that once they have ticked the boxes in the checklist and filled out the numbers in the flowchart, salvation is theirs – they are "CONSORT compliant"

- I hope CONSORT group would agree: this is not true

- For editor (and reader) the devil is in the details!

What is outcome reporting bias ("ORB")?

- An area addressed by CONSORT that's receiving greater attention from journals and researchers
- ORB is a form of publication bias
- Occurs when statistically significant findings are more likely to be reported in published papers
- Authors, reviewers and editors can all contribute to the problem (and help address it)
- Some journals – including PLoS journals – now ask for full protocols for submitted RCTs
- On PLoS Medicine – check outcomes reported in the paper against those in the protocol
- Frequently ask authors to add results for these outcomes to the paper and / or add explanations about outcome changes



- Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan A-W, et al. (2008) Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias. PLoS ONE 3(8): e3081.

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Using CONSORT guidance in peer review: specific examples

- *Item 6a. Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed*

- "All outcome measures, whether primary or secondary, should be identified and completely defined. The principle here is that the information provided should be sufficient to allow others to use the same outcomes. When outcomes are assessed at several time points after randomisation, authors should also indicate the pre-specified time point of primary interest."

Results reporting – outcome definition and analysis

Example of paper submitted to PLoS journal with a fully completed CONSORT flowchart and checklist

This feedback was sent from editor to authors:

"In the objective, method, results and discussion sections, the authors should clearly indicate and separate the following:

a. the primary objective of this trial: i.e., assessment of beneficial effect at 6 months on the [redacted],

b. the secondary objectives of the study: i.e., assessment of secondary outcomes and safety…

c. the ancillary exploratory analyses…

2) The analyses performed should be a true ITT analyses with data for all patients randomised analysed.

3) The authors report the results on a subgroup of patients divided according to age. Was the randomisation stratified on age?

4) The reporting of the results should follow the CONSORT recommendations by reporting the number of patients with data, summary statistics in each arm (mean [SD] or median [IQR] but also between group differences such as difference in means with 95% CI"

Using CONSORT guidance in peer review: specific examples

- *Item 18. Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory*

- "Multiple analyses of the same data create a risk for false positive findings. Authors should resist the temptation to perform many subgroup analyses. Analyses that were prespecified in the trial protocol are much more reliable than those suggested by the data, and therefore authors should report which analyses were prespecified. If subgroup analyses were undertaken, authors should report which subgroups were examined, why, if they were prespecified, and how many were prespecified. Selective reporting of subgroup analyses could lead to bias"

Using CONSORT guidance in peer review: specific examples

- *Item 18. Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory*

- Example
- "We performed a double-blind randomised placebo-controlled trial of pralidoxime chloride (2 g loading dose over 20 min, followed by a constant infusion of 0.5 g/h for up to 7 d) versus saline in patients with organophosphorus insecticide self-poisoning. Mortality was the primary outcome; secondary outcomes included intubation, duration of intubation, and time to death."
- "An exploratory analysis using Cox's regression investigated the effects of potentially important prognostic factors such as percentage of aged acetylcholinesterase on admission and OP concentration on admission"
- Eddleston M, Eyer P, Worek F, Juszczak E, Alder N, et al. (2009) Pralidoxime in Acute Organophosphorus Insecticide Poisoning—A Randomised Controlled Trial. PLoS Med 6(6): e1000104. doi:10.1371/journal.pmed.1000104

Using CONSORT in publication

- Optional template for authors, using CONSORT items as headings for structured writeup of the paper
- Available for authors on all PLoS journals but most heavily used on *PLoS Medicine, PLoS ONE*
- Sent to authors when a revision is invited
- Authors can use components that work for them – in addition to the CONSORT checklist and flowchart
- Works best for primary papers (ie reporting main results of RCT); less so for exploratory / ancillary papers
- For published papers, CONSORT flowchart, checklist and protocol all included alongside as figures / supporting information

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PLoS one

Effect of Peer Health Workers on AIDS Care in Rakai, Uganda: A Cluster-Randomized Trial

Larry W. Chang[1]*, Joseph Kagaayi[2], Gertrude Nakigozi[2], Victor Ssempijja[2], Arnold H. Packer[3], David Serwadda[2], Thomas C. Quinn[1,4], Ronald H. Gray[5], Robert C. Bollinger[1], Steven J. Reynolds[1,4]

1 Division of Infectious Diseases, Johns Hopkins School of Medicine, Baltimore, Maryland, United States of America, 2 Rakai Health Sciences Program, Kalisizo, Uganda, 3 Johns Hopkins University, Baltimore, Maryland, United States of America, 4 Laboratory of Immunoregulation, Division of Intramural Research, National Institute for Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, United States of America, 5 Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America

Abstract

Background: Human resource limitations are a challenge to the delivery of antiretroviral therapy (ART) in low-resource settings. We conducted a cluster randomized trial to assess the effect of community-based peer health workers (PHW) on AIDS care of adults in Rakai, Uganda.

Methodology/Principal Findings: 15 AIDS clinics were randomized 2:1 to receive the PHW intervention (n = 10) or control (n = 5). PHW tasks included clinic and home-based provision of counseling, clinical, adherence to ART, and social support. Primary outcomes were adherence and cumulative risk of virologic failure (>400 copies/mL). Secondary outcomes were virologic failure at each 24 week time point up to 192 weeks of ART. Analysis was by intention to treat. From May 2006 to July 2008, 1336 patients were followed. 444 (33%) of these patients were already on ART at the start of the study. No significant differences were found in lack of adherence (<95% pill count adherence risk ratio [RR] 0.55, 95% confidence interval [CI] 0.23–1.35; <100% adherence RR 1.10, 95% CI 0.94–1.30), cumulative risk of virologic failure (RR 0.81, 95% CI 0.61–1.08) or in shorter-term virologic outcomes (24 week virologic failure RR 0.93, 95% CI 0.65–1.32; 48 week, RR 0.83, 95% CI 0.47–1.48; 72 week, RR 0.81, 95% CI 0.44–1.49). However, virologic failure rates ≥96 weeks into ART were significantly decreased in the intervention arm compared to the control arm (96 week failure RR 0.50, 95% CI 0.31–0.81; 120 week, RR 0.59, 95% CI 0.22–1.60; 144 week, RR 0.39, 95% CI 0.16–0.95; 168 week, RR 0.30, 95% CI 0.097–0.92; 192 week, RR 0.067, 95% CI 0.0061–0.71).

Conclusions/Significance: A PHW intervention was associated with decreased virologic failure rates occurring 96 weeks and longer into ART, but did not affect cumulative risk of virologic failure, adherence measures, or shorter-term virologic outcomes. PHWs may be an effective intervention to sustain long-term ART in low-resource settings.

Trial Registration: ClinicalTrials.gov NCT00675389

Citation: Chang LW, Kagaayi J, Nakigozi G, Ssempijja V, Packer AH, et al. (2010) Effect of Peer Health Workers on AIDS Care in Rakai, Uganda: A Cluster-Randomized Trial. PLoS ONE 5(6): e10923. doi:10.1371/journal.pone.0010923

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* E-mail: lchang88@jhmi.edu

Introduction

The provision of antiretroviral therapy (ART) in low-resource settings entails substantial challenges due to human resource limitations [1]. One of the main strategies advocated by the World Health Organization (WHO) and the United States President's Emergency Plan for AIDS Relief (PEPFAR) to address this crisis is through task shifting, the rational redistribution of tasks among health workforce teams from higher trained providers to those who require less training [2]. Community health workers (CHWs) are a key cadre to whom tasks can be shifted; however, there is limited trial-based evidence on their effectiveness in improving AIDS care outcomes [2,3].

Community-based peer health workers (PHWs) are people living with HIV (PLHIV) and may potentially be a valuable type of CHW. Peers have been used effectively in HIV/AIDS programs in low-resource settings, typically as peer educators [4], and psychosocial support using peers has been recommended by the WHO for all PLHIV [5]. However, PHWs could deliver more care-oriented services in addition to counseling, education, and social support, and may therefore provide one strategy to mitigate the human resource crisis.

The Rakai Health Sciences Program (RHSP) is located in the rural Rakai District in southwest Uganda. Since June 2004, PEPFAR has enabled RHSP to provide ART via a decentralized, mobile clinic approach. In an operational and implementation research effort to evaluate the role of task shifting with PHWs at RHSP [6,7], we conducted a cluster-randomised trial of the effect of PHWs on adult AIDS care outcomes [8]. Descriptive pilot data were previously presented [9], and this study reports trial

Where are CONSORT items reported?

- Trial registration (item 23)
- Funding (item 25)

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outcomes. Our primary hypothesis was that, compared to patients in control communities, patients on ART in communities with PHWs will have improved adherence and fewer virologic failures.

Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Protocol S1 and Checklist S1.

Ethics Statement

The trial was approved by institutional review boards at the Uganda Virus Research Institute, the Uganda National Council for Science and Technology, Johns Hopkins University, and the Western Institutional Review Board (Olympia, WA). Informed consent was not obtained for this study as the institutional review boards agreed that (i) PHWs were program staff performing routine care functions, and (ii) only de-identified programmatic data would be analyzed by community of randomization, and therefore no informed consent was required.

Study Setting

The Rakai district in southwestern Uganda has a population of approximately 460,000 persons in an area of about 5000 square kilometers. In June 2004, RHSP/PEPFAR began providing ART through a mobile clinic program operating in 15 non-overlapping catchment areas (clusters) throughout the district. The mobile clinic model consisted of medical staff traveling from a central facility to designated government health clinics in each catchment area biweekly. In between clinic days (13 out of 14 days), patients' options for accessing care were limited and included traveling to a central facility, calling an RHSP mobile phone hotline (with call cost paid by caller) or toll-free warmline (similar to a hotline but staffed only during clinic hours), or visiting non-RHSP care facilities and providers [10].

Participants

This trial was conducted between May 2006 to July 2008 and comprised all adult patients at the 15 mobile clinic sites who were either already on ART at the start of the trial or were started on ART at any time during the trial. About half (53%) of these patients were referred to the clinic from previous or current RHSP studies. All of these studies have recruited participants representative of Rakai District as a whole [11]. The remaining participants (47%) were "walk-ins" as any Rakai resident could come to these clinics and receive HIV counseling, testing, and care. Eligibility criteria for starting ART was a CD4 count ≤250 or WHO Stage IV illness [12]. All care and medications were provided free of charge.

PHW Intervention (Arm A)

In addition to the usual standard of care at all clinic sites, Arm A clinics received the PHW intervention. The general approach to the design and implementation of this intervention was pragmatically-oriented, meaning that a general framework for PHW recruitment, training, tasks, and monitoring was developed, but the intervention was allowed to adapt to needs and problems which arose, e.g. arranging for a home visit to occur at a workplace if so requested by a patient [8]. Criteria for becoming a PHW included being a PLHIV on ART, good ART adherence for at least six months, and literacy. PHWs were nominated by fellow patients at each clinic site with final approval by RHSP staff if they met all qualifications. PHWs received a two day residential training on basic HIV pathogenesis, prevention, treatment, adherence counseling, performing pill counts, protecting patient confidentiality, and filling out a home visit form. Trainers included RHSP staff and experienced PHWs from an urban-based Ugandan ART program [13]. At the clinic, PHW tasks included providing ART counseling and support in group and individual sessions. For their home visit tasks, PHWs were initially assigned about 15 patients each who were visited biweekly. At these visits, PHWs were tasked to record on a standardized form a review of symptoms, a patient self-report of adherence, and to perform and record a pill count. PHWs were asked to counsel and educate their patients on ART adherence and general HIV/AIDS-related issues during these home visits. If patients were thought to need urgent care, PHWs were asked to alert RHSP staff and facilitate transfer to a higher level of care. PHWs returned completed forms to subsequent clinic sessions where they were added to patient charts for provider review. To assist with their duties and encourage retention, PHWs were each given a bicycle, identifying t-shirts, basic supplies, and an initial monthly allowance of about 12.5 USD. Day-to-day supervision of PHW activities were largely performed by a single RHSP staff member working part-time.

Control Group (Arm B)

The control arm continued with the usual standard of care. However, standard of care did change over the study period, as a number of changes unrelated to the PHWs were subsequently implemented by RHSP in both the PHW and control arms. These programmatic changes included a peer educator program to promote use of preventive care services in mid-2006, the use of viral load results to guide care in late 2006, more focused ART-related health messaging in early 2007, and the use of enhanced adherence counseling, chart stickers to help identify patients failing virologically, and second-line ART provider talks in mid- to late 2007.

Mobile Phone Support Intervention Substudy (Arm A^1 and A^2)

As a substudy, PHW intervention areas were also randomized 2:1 to receive a mobile phone support intervention (Arm A^1, n = 4 clusters) or not (Arm A^2, n = 6 clusters). PHWs randomized to the mobile phone intervention were each given a mobile phone and, in addition to their usual responsibilities, were tasked to use text messaging to send home visit data back to the central clinic to be reviewed by centralized staff. PHWs could also call providers with questions or concerns [10]. Detailed results from this substudy will be presented elsewhere.

Procedures

We used an unrestricted randomization process. The 15 mobile clinic sites were randomized 2:1 to receive the PHW intervention (Arms A, n = 10 clusters) or control (Arm B, n = 5 clusters). We assigned clusters using unmatched, unrestricted random allocation by a drawing of lots. Study investigators (LWC, JK) generated the allocation sequence and implemented the randomization. This study was open label and unblinded.

Outcomes

The primary outcomes included adherence (pill counts) and cumulative risk of virologic failure (any failure during follow-up period equaling failure). Secondary outcomes were virologic failure at each 24 week time point up to 192 weeks of antiretroviral therapy, mortality, lost to follow-up, and CD4 change at 24 and 48 weeks of ART. A summary clinic pill count was calculated by dividing the number of pills taken over the study period by the sum

Where are CONSORT items reported?

Study setting (item 4b)

Participants (item 4a)

Interventions (item 5)

Outcomes (item 6a)

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Journal experiences of CONSORT

- *PLoS Medicine* is a CONSORT endorser (and we try hard to be an implementer!)
- But making sure that every paper we publish fully adheres to CONSORT is another matter
- Despite the simplicity and usability of CONSORT, substantial editorial input is often needed to help authors understand and use the guidance for their particular study
- CONSORT instruments (checklist, flowchart) now well accepted and used by authors
- Most authors not yet ready to try template-based reporting
- We tried enforcing this for a while but it did not take off

What are the barriers?

- Lack of awareness of appropriate standards for reporting
- Language?
- Lack of time – for authors, editors, reviewers
- Authors need to get the paper published as quickly as possible
- Reluctance among researchers to admit that not all went as planned – eg outcome changes during the trial

Using CONSORT: what are the advantages and opportunities?

For authors:

- Adhering to CONSORT upfront means your paper will go straight through to the editor's desk
- Clearly reported papers go through peer review faster and with fewer revisions. Quicker, easier trip through copyediting
- We can't guarantee the decision will be different (as this may well hinge on the importance of the question and quality of the study)

For editors / guideline developers:

- Look at guidance for exploratory or ancillary papers?
- Look at reporting standards for non randomized trials?

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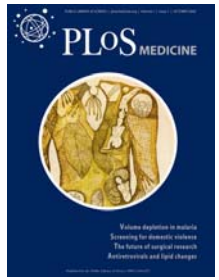
PLoS Medicine
October, 2004



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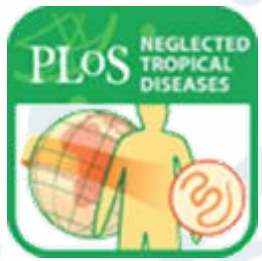

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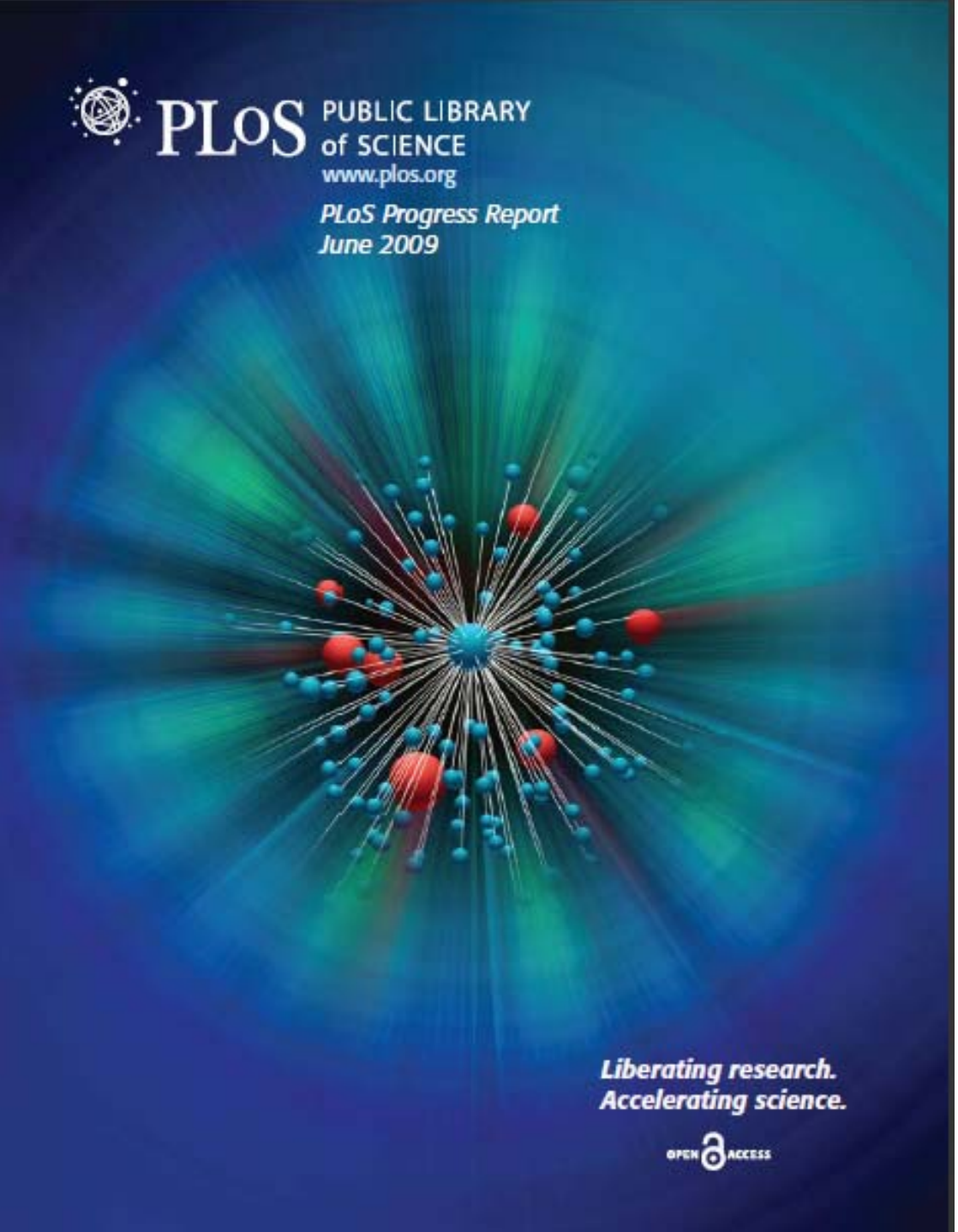

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