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Randomized Controlled Trials of Electronic Health Record Interventions: Design, Conduct, and Reporting Considerations

Mark J. Pletcher, MD, MPH; Valerie Flaherman, MD, MPH; Nader Najafi, MD; Sajan Patel, MD; Robert J. Rushakoff, MD; Ari Hoffman, MD; Andrew Robinson, BS; Russell J. Cucina, MD, MS; Charles E. McCulloch, PhD; Ralph Gonzales, MD, MS; and Andrew Auerbach, MD

Electronic health record (EHR) systems can be configured to deliver novel EHR interventions that influence clinical decision making and to support efficient randomized controlled trials (RCTs) designed to evaluate the effectiveness, safety, and costs of those interventions. In designing RCTs of EHR interventions, one should carefully consider the unit of randomization (for example, patient, encounter, clinician, or clinical unit), balancing concerns about contamination of an intervention across randomization units within clusters (for example, patients within clinical units) against the superior control of measured and unmeasured confounders that comes with randomizing a larger number of units. One should also consider whether the key computational assessment components of the EHR intervention, such as a predictive algorithm used to target a subgroup for decision support, should occur before randomization (so that only 1 subgroup is randomized) or after randomization (including all subgroups). When these components are applied after randomization, one must consider expected heterogeneity in the effect of the differential decision support across subgroups, which has implications for overall impact potential, analytic approach, and sample size planning. Trials of EHR interventions should be reviewed by an institutional review board, but may not require patient-level informed consent when the interventions being tested can be considered minimal risk or quality improvement, and when clinical decision making is supported, rather than controlled, by an EHR intervention. Data and safety monitoring for RCTs of EHR interventions should be conducted to guide institutional pragmatic decision making about implementation and ensure that continuing randomization remains justified. Reporting should follow the CONSORT (Consolidated Standards of Reporting Trials) Statement, with extensions for pragmatic trials and cluster RCTs when applicable, and should include detailed materials to enhance reproducibility.

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For author affiliations, see end of text.

Electronic health record (EHR) systems are now central to health care delivery and provide major new opportunities for delivering point-of-care clinical decision support (CDS) that can improve health care delivery and health outcomes (1). Designing effective EHR interventions, however, remains a major challenge. It is easy to build clinician-facing alerts, but far less easy to modify ordering behavior, and it is unfortunately much too easy to disrupt workflows, induce alert fatigue, and reduce clinician efficiency and satisfaction (1–5). Even when an intervention effectively modifies clinician behavior, it may not have the intended downstream impact on health outcomes and may also have unintended consequences (6).

Although many options exist for evaluating the impact of interventions designed to improve care in a health care system, the randomized controlled trial (RCT) generally provides the highest level of evidence. Overall, however, RCTs are uncommon in the context of quality improvement because of the burden and disruption to patient care workflows imposed by RCT-related tasks, such as obtaining informed consent from patients, implementing a randomization scheme, delivering different interventions to different groups of patients or clinicians according to randomization assignment, and collecting data at baseline and follow-up.

Electronic health record systems can now support these RCT-related tasks. In some cases, an RCT may be embedded in the EHR and health care delivery system such that it is invisible to clinicians and does not disrupt clinical workflows in any way other than the desired intervention. The hope of achieving continual and evidence-based quality improvement with manageable health care delivery system overhead may entice health care institutions to support development of learning health systems that truly integrate knowledge generation and health care delivery, as envisioned by the National Academy of Medicine and others (7–10).

Many special issues arise, however, in the design, conduct, and reporting of RCTs of EHR interventions. This article addresses these issues, contrasting RCTs of EHR interventions with traditional RCTs, and provides recommendations for study design and implementation. We illustrate our recommendations by using an RCT conducted at our institution to test the effectiveness of a dynamic evidence-based admission order set for chronic obstructive pulmonary disease (COPD). We end with specific recommendations for additions to the CONSORT (Consolidated Standards of Reporting Trials) statement to enhance reporting of RCTs of EHR interventions.

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Table. Summary of Recommendations for Study Design and Implementation and Reporting of RCTs of EHR Interventions, Including Additions to CONSORT

Issue	Recommendation	
	Study Design and Implementation	**Reporting**
Handling RCT mechanics using the EHR	Automate eligibility assessment, enrollment, randomization, conditional delivery of EHR interventions, and follow-up data collection using the EHR system	Provide computer code or other technical documentation about implementation of eligibility rules, outcome definitions, and other key computation to enhance reproducibility*
Describing the EHR intervention	NA	Include screenshots or screen-capture videos to illustrate design features of the intervention and algorithms or code, when possible*
Human subjects issues	Request protocol review from your IRB even if an RCT of an EHR intervention may be considered quality improvement; waiving informed consent may be appropriate in some studies	Report whether your IRB approved the study, provided a waiver of informed consent, or provided a determination that the project was not human subjects research
Unit of randomization	Consider the potential advantages and disadvantages of cluster randomization, which may depend on how teams are structured and other organizational factors	Report the unit of randomization and rationale for your choice in the context of how health care delivery is organized at your institution
Randomization procedure	Use true randomization rather than pseudorandomization (e.g., using day of the week or an even/odd medical record number)	Standard CONSORT reporting
Heterogeneity of intervention effects	Plan (and power your trial) for heterogeneity of intervention effects when the intervention delivers different clinical decision support to different subgroups of your randomized patient sample	Report subgroup analyses and interactions with clear labeling of which were prespecified for analysis of expected heterogeneity
Interim monitoring and oversight	Include clinical and operations leaders on data and safety monitoring boards (along with trialists and statisticians) so that interim monitoring and decision making is pragmatic and useful for the institution and research team	Report prespecified plans for interim monitoring and the rationale for termination and decisions regarding implementation (which may include pragmatic local considerations)
Outcome reporting	Assess process outcomes along with health outcomes (both intended and adverse); be aware of limitations of EHR data for complete and consistent outcome measurement	Report all analyzed outcomes, clearly indicating which were prespecified, and limitations in ascertainment of outcomes that might occur external to (or unmeasured within) the accessible health care delivery system

CONSORT = Consolidated Standards of Reporting Trials; EHR = electronic health record; IRB = institutional review board; NA = not applicable; RCT = randomized controlled trial.
* This item is an addition to CONSORT. The other items in the Reporting column represent special considerations for existing CONSORT items relevant for reporting of RCTs of EHR interventions.

Design and Implementation of RCTs of EHR Interventions

Mechanics of Patient Enrollment, Randomization, and Data Collection

At a minimum, RCTs require identification and enrollment of patients eligible for the study, assignment to different intervention groups, delivery of the specified interventions according to the assignment, and follow-up data collection. These mechanics can all be accomplished via programming of EHR systems (Table), though challenges arise.

Eligibility assessment and enrollment may be accomplished automatically and in real time by using EHR systems, which are designed to track patients over time and evaluate collected data according to complex logical operations and mathematical algorithms. Operationalizing eligibility decisions in real time, however, requires use of available data, which is often messy without manual curation and incomplete owing to variability in clinical decisions and documentation, especially at the moment when eligibility determinations must be made. In our sample RCT, the target population was patients admitted for COPD, and the investigators needed to determine eligibility on admission so that the evidence-based COPD orders could be dynamically added to the admission order set. To do this, however, required assessing eligibility at a moment when the diagnosis of COPD is often uncertain or unclearly documented. The investigators used retrospective data to fit a logistic model that predicted eventual COPD discharge diagnosis by using emergency department data (and past history). Accuracy of the logistic model was imperfect but was judged to be adequate to guide autoinclusion of the orders to clinicians in the intervention group. The investigators chose a cut-point in the predicted probability of COPD as an eligibility threshold for enrollment in the RCT that struck a balance between maximizing sensitivity (so that they missed few patients with COPD) and maximizing specificity (to minimize adding COPD orders for patients without COPD). The RCT will assess how well this sys-

tem works for improving health outcomes in these patients.

Randomization to different groups of an RCT, with stratification and blocking to balance sample size between randomization groups within strata, can also be programmed to occur within an EHR system. True randomization using a random-number generator should be implemented, rather than a surrogate, such as day of week or odd/even medical record number, to ensure unpredictability and avoid the induction of confounding from associated factors (for example, different types of patients being admitted over the weekend). Adaptive randomization (for example, modifying the randomization ratio over time) may be easier to implement in RCTs of EHR interventions than in traditional RCTs because of the "closed loop" system: That is, EHR data parameters used for adaptive computation may be generated automatically and readily available within the system. In our sample RCT, the investigators did not stratify but did use blocked randomization to balance the number of patients with COPD who were randomly assigned to the dynamic order set or usual care.

Follow-up data collection occurs naturally in EHRs whenever patients have contact with the health care delivery system, and these data can be used to define outcome measures for an RCT. For any RCT aiming to assess improvements in health care delivery from an EHR intervention, one should consider measuring not only the intended health consequences of the intervention, but also "balancing outcomes" that assess potential adverse and unintended health consequences (at least those that can be anticipated), as well as process measures (for example, ordering behavior) and effect on clinician workflow or workload, health care utilization, and costs. Some important outcomes are clearly defined and automatically recorded (for example, in-hospital death, length of stay), whereas others are not consistently available (for example, patient-reported outcomes) or rely on active documentation that might not always occur or be in a format amenable to analysis. Furthermore, whereas significant clinical events occurring in the hospital before discharge are likely to be captured completely, clinical events occurring outside the hospital may not. Linking EHR data across institutions or with claims data (for example, from Medicare or commercial insurers) is sometimes possible, but these data are usually not available, restricted to clinical use, or limited in scope. It will often be difficult in this context to even assess whether acceptably high levels of complete data (such as >90%) are attained. Furthermore, problems with bias from incomplete follow-up data collection, especially during outpatient follow-up (for example, due to EHR data collection that is triggered by clinical events instead of being systematic and complete) cannot be overcome with more data or larger sample sizes. These limitations in EHR-based data collection are critical to consider during study design, implementation, and reporting. In our sample RCT, investigators measured clinician ordering behavior (to see whether the dynamic COPD orders were used), in-hospital health outcomes (such as intubation and mortality), and postdischarge readmission rates, acknowledging the limitation that some readmission events at other hospitals would be missed.

Design Options for RCTs

Although nonrandomized studies, pre–post comparisons, different types of trials, and more complex variants (for example, stepped-wedge designs [11]) have their advantages (12), parallel-design RCTs typically offer superior control of co-occurring secular trends and stronger causal inference. Below are some of the design issues that commonly arise for parallel-group RCTs of EHR interventions.

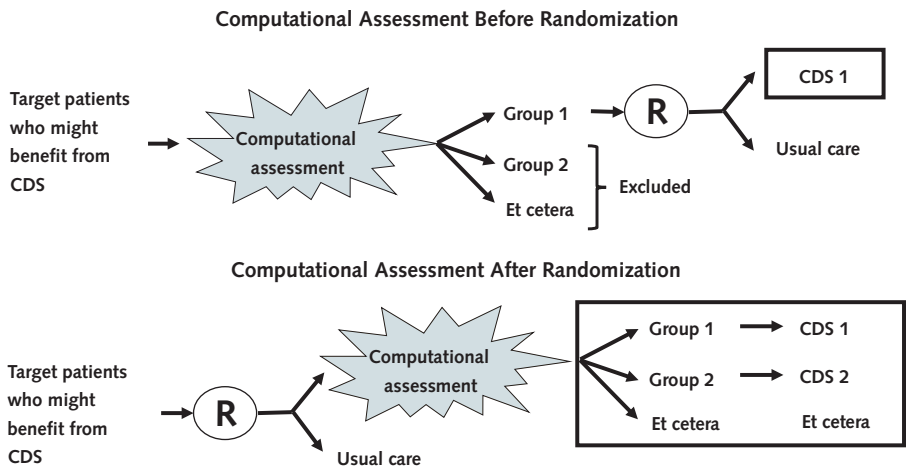
Unit of Randomization

Randomization of individual persons is standard practice in RCTs, but this may not be the natural unit of randomization for an EHR intervention. It is often desirable to randomize units that are lower in the hierarchical structure of health care delivery, such as patient encounters or even clinical events within patient encounters, or to randomize clusters, such as clinicians (who treat multiple patients), clinical teams, wards, clinics, and other clinical units within a health care institution so that all patients within a cluster are exposed to the assigned intervention. Because health care delivery is naturally organized in clusters, cluster randomization has the advantage of eliminating within-cluster contamination (such as contamination between patients cared for by a single clinician or clinicians working on a team).

Cluster randomization has 4 distinct disadvantages. First, statistical power may be lower per individual patient or encounter owing to design effects from intracluster correlation (13). Second, if there are few clusters or the clusters are very heterogeneous, substantial imbalance in measured or unmeasured confounders may occur, limiting the benefits of randomization. Third, programming EHR-delivered interventions that are conditional on randomization assignment of clusters can be complex, given attribution issues and shifting clinical responsibilities for clinical teams or individual clinicians over time (for example, clinicians on night float). Finally, analysis of clinical outcomes can be challenging even when attribution is clear, because outcomes usually occur at the level of the individual patient, and individual patients may be exposed to clinicians (or other factors) associated with more than 1 randomization unit cluster.

For example, in our sample RCT, the investigators considered various cluster RCT designs. The investigators considered randomizing admitting teams, but implementation was not feasible because team structure and attribution are not entirely specified within the EHR. Further, with only a limited number of distinct and heterogeneous team units, the investigators were concerned about imbalance between groups, even with randomization. Randomizing clinicians would have eliminated contamination within the group of patients cared for by each clinician but would also have reduced the number of randomized units. Ultimately, they opted for randomization of hospitalization encounters and will attempt to account for cluster-level

Figure. Design options for RCTs of EHR interventions.



CDS = clinical decision support; EHR = electronic health record; R = randomization; RCT = randomized controlled trial. **Top.** Computational assessment occurs before randomization and determines the subset of the target population that is randomized. **Bottom.** Computational assessment occurs *after* randomization and determines what CDS is delivered.

nonindependence and potential contamination within those clusters in the analysis phase of the project.

Computational Assessment Before or After Randomization

Electronic health record interventions typically deliver CDS informed by a computational assessment of available data. Computational assessments ranging in complexity from simple decision rules to elaborate mathematical functions are often used to identify different groups of patients from among target patients, for whom different CDS is warranted. The computational assessment, which is a key part of the added value of EHR interventions, can be positioned before or after randomization in an RCT (**Figure**).

In our sample RCT, the investigators developed a logistic regression model to assess likelihood of an eventual COPD diagnosis. This computational assessment was used before randomization to categorize patients being admitted to the hospital as likely to have COPD (group 1 in the top panel of the **Figure**) or not (group 2 in the bottom panel of the **Figure**). Only patients in group 1 who were likely to have COPD were randomly assigned to receive the CDS intervention (dynamic evidence-based COPD orders) or usual care; group 2 patients were excluded from the RCT. Alternatively, the investigators might have opted to place the computational assessment after randomization. In this case, all admitted patients would have undergone random assignment, followed by computational assessment (logistic modeling) and delivery of the dynamic COPD orders to group 1. In this alternate study design, patients in group 2 would be included in the RCT and might receive usual care or some other active CDS relevant to patients at lower likelihood of having COPD (for example, active discouragement of steroid orders—CDS 2 in the bottom panel of the **Figure**).

This decision has important implications. By placing the computational assessment before randomization, the investigators excluded a large proportion of admitted patients from the parallel-group RCT analysis (patients with low likelihood of COPD). This design, therefore, cannot directly assess overall impact of the computational assessment, which is certain to miss some patients with COPD and could have indirect effects on patients without COPD. The alternative design would have evaluated the overall impact of the intervention on the entire target population of admitted patients. This design, however, would have included group 2 in the study, even though the effect of the intervention would be expected to differ from that in group 1 (for example, group 2 might be discouraged, rather than encouraged, to order steroids). Because the effect of the intervention is expected to differ, any simple unstratified analysis of the full RCT sample will dilute and obscure the intended effect of CDS 1 (which is only delivered to group 1), and likewise for CDS 2. Stratified or subgroup analyses are required to clearly describe these heterogeneous intervention effects. Because heterogeneity of intervention effect is an expected feature of this type of study design (bottom panel of the **Figure**), it must be accounted for in planning (effect size dilution may lead to larger required sample size), implementation (stratified randomization), analysis (subgroup/interaction testing), and reporting (clearly label prespecification of group-specific analyses) (**Table**).

Ethics and Institutional Review Board Oversight

Because RCTs are by nature experimental and expose patients to interventions that may affect their health, ethical considerations are paramount. Traditional human subjects research ethics (14, 15) and regulations (16) generally are based on an assumption that research activities can be distinguished from clinical practice, but a true

learning health system marries the 2, simultaneously implementing health care improvement and generating knowledge (for example, through RCTs of EHR interventions). This places new demands on traditional ethical and regulatory frameworks (17–20).

A particular challenge for RCTs of EHR interventions is the traditional requirement for informed consent in human subjects research. Prospectively obtaining explicit written informed consent is not practicable or even possible for many RCTs of EHR interventions that are fully automated and occurring in real time during clinical care. According to the Common Rule (16), a waiver of informed consent may be justified if it is not practicable, and if the research exposes human subjects to minimal risk. These criteria may be met when a putative quality improvement intervention is compared against usual care (as in randomized quality improvement trials [18]). On the other hand, these criteria may not be met when EHR interventions deviate from standards of care, supersede clinician judgment, or require weighing an individual patient's valuation of outcome tradeoffs, or when the RCT evaluation itself imposes extra burdens (for example, for extra data collection) on patients or clinicians. In any case, we recommend that RCTs of EHR interventions be reviewed by institutional review boards, which can help evaluate whether a waiver of informed consent is justified, and ensure that the human rights and safety of patients enrolled in these RCTs are adequately protected.

Data and Safety Monitoring and Statistical Considerations

Randomized controlled trials with human subjects obligate investigators to a time-sensitive responsibility to monitor, evaluate, and compare outcomes between randomization groups. Ultimately, the goal must be to complete the implementation decision and either implement fully (for all patients, not just those in 1 of the groups) or abandon the intervention. This decision should certainly be evaluated at the end of the planned RCT recruitment but may also be considered periodically during the study—for example by an independent data and safety monitoring board (DSMB), to ensure that continuing randomization is still warranted. Unlike traditional DSMBs, which consider eventual generalizable scientific value generated by the RCT (along with patient safety) to be paramount, DSMBs for randomized quality improvement trials and other RCTs of EHR interventions focus on local implementation decision making. To achieve this objective, DSMBs for these RCTs should include clinical and operational leaders at the local institution (along with clinical trialists and statisticians); also, these DSMBs are less bound to traditional statistical significance thresholds and conservative stopping rules to maintain α for a final statistical hypothesis test, though they still must consider the expected swings of random variation before making an early stopping decision. In addition, the fact that most of the costs of RCTs of EHR interventions are upfront allows for more fluid and lower-stakes decision making about sample size (for example, to continue an RCT for longer than had originally been planned) and makes Bayesian and adaptive approaches to interim monitoring attractive (21–23). As an example, our sample RCT was stopped early after the DSMB considered posterior estimates of benefit and harm (under a range of priors) from a formal Bayesian analysis.

Reporting RCTs of EHR Interventions

Although RCTs of EHR interventions are ideally designed as pragmatic trials that directly inform local decision making, dissemination of both positive and negative results helps advance the relatively new science of EHR-based CDS and allows health care organizations to learn from each other's successes and failures. To ensure consistency of reporting, RCTs of EHR interventions should be registered in ClinicalTrials.gov. Manuscripts should follow the CONSORT (Consolidated Standards of Reporting Trials) Statement (24), as well as the CONSORT extension for pragmatic trials (25), assuming that generating evidence to inform local implementation decision making is a primary goal of the study. The CONSORT extension for cluster randomized trials (26) is relevant if a cluster RCT design is chosen. Though not designed for RCTs in particular, the STARE-HI (Statement on Reporting of Evaluation Studies in Health Informatics) (27) has a useful focus on reporting the specific details of study context, which are inherently relevant to whether an evaluation of local effectiveness might translate to another health care delivery context.

Reports of RCTs of EHR interventions should include additional elements not specified in CONSORT or published extensions (**Table**). For example, to enhance RCT reproducibility, publications should include computer code or equivalent technical documentation of how the mechanics of the RCT were implemented. Although EHR implementations differ across institutions (even within vendor), the code will often clarify implementation details and may be at least partially reusable. It is also critical to describe the EHR intervention in detail; this will be greatly enhanced by including computer code and screenshots or screen-capture videos of the EHR intervention in supplemental materials. If vendors restrict publication of images depicting proprietary systems or authors are concerned about protecting intellectual property (for example, if they wish to commercialize an EHR intervention), carefully limited images may still be publishable. A detailed description of the EHR intervention will be essential and should be the minimum reporting requirement. Electronic health record interventions that use resources external to the EHR, such as Substitutable Medical Applications and Reusable Technologies (SMART) applications using the Fast Healthcare Interoperability Resources (FHIR) standard (28), may be particularly easy to reproduce across institutions. Although RCTs of EHR interventions may often be considered quality improvement projects, authors should still report results of a review by their institutional review board, even if the result is a formal

declaration that the RCT is not considered to be human subjects research.

Finally, post hoc analyses are often conducted by project teams (for example, additional outcomes, subgroup analyses, or alternative statistical approaches to interim monitoring) to facilitate decision making about implementation. These types of analyses should be clearly labeled as post hoc and distinguished from prespecified hypothesis testing.

Discussion

Federal legislation a decade ago ushered in a new era of EHR systems, but the promises of better clinical care from implementation of the technology have not yet been fully realized (29). Designing EHR modifications to improve clinical care and then carefully testing effectiveness of those EHR interventions through RCTs will be critically important to ensure that well-intended modifications achieve their intended results without unintended consequences. Design and implementation of RCTs of EHR interventions can be a challenge, but with adequate infrastructure and local expertise, these RCTs can be relatively efficient. These studies remain uncommon, but they are starting to appear in the literature (30–36). Increasing the number of rigorously conducted RCTs of EHR interventions generating evidence-based EHR-enabled quality improvement in health care systems across the country will help the United States make progress toward the National Academy of Medicine's vision of a learning health system.

From University of California, San Francisco, San Francisco, California (M.J.P., V.F., N.N., S.P., R.J.R., A.H., A.R., R.J.C., C.E.M., R.G., A.A.).

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Corresponding Author: Mark Pletcher, MD, MPH, University of California, San Francisco, Box 0560, 550 16th Street, Mission Hall, 2nd Floor, San Francisco, CA 94143; e-mail, mark.pletcher@ucsf.edu.

Current Author Addresses: Dr. Pletcher: University of California, San Francisco, Box 0560, 550 16th Street, Mission Hall, Second Floor, San Francisco, CA 94143.

Dr. Flaherman: University of California, San Francisco, Box 0503, 3333 California Street, 245, San Francisco, CA 94143.

Drs. Najafi, Patel, and Hoffman: University of California, San Francisco, Box 0131, 533 Parnassus Avenue, 127B, San Francisco, CA 94143.

Dr. Rushakoff: University of California, San Francisco, Box 1616, 2200 Post Street, C4-30, San Francisco, CA 94143.

Mr. Robinson and Dr. Gonzales: University of California, San Francisco, Box 0558, 550 16th Street, San Francisco, CA 94143.

Dr. Cucina: University of California, San Francisco, Box 0914, 350 Parnassus Avenue, 210F, San Francisco, CA 94143.

Dr. McCulloch: University of California, San Francisco, Box 0560, 550 16th Street, 2430, San Francisco, CA 94143.

Dr. Auerbach: University of California, San Francisco, Box 0131, 533 Parnassus Avenue, 131, San Francisco, CA 94143.

Author Contributions: Conception and design: M.J. Pletcher, S. Patel, R.J. Rushakoff, A. Robinson, R.J. Cucina, A. Auerbach.

Analysis and interpretation of the data: V. Flaherman, S. Patel, R.J. Rushakoff, C.E. McCulloch.

Drafting of the article: M.J. Pletcher, N. Najafi, A. Hoffman, A. Auerbach.

Critical revision of the article for important intellectual content: M.J. Pletcher, V. Flaherman, S. Patel, A. Hoffman, R.J. Cucina, C.E. McCulloch, R. Gonzales, A. Auerbach.

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Provision of study materials or patients: S. Patel, A. Hoffman, R.J. Cucina.

Statistical expertise: C.E. McCulloch.

Obtaining of funding: R.J. Cucina, A. Auerbach.

Administrative, technical, or logistic support: A. Robinson, R.J. Cucina, R. Gonzales, A. Auerbach.

Collection and assembly of data: S. Patel, R.J. Rushakoff, A. Robinson.

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