Users Guide to Designing N-of-1 Trials

Chapter 5

Information Technology (IT) Infrastructure for N-of-1 Trials

Draft for Comment

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Decisions in medical science are primarily driven by applying the results of parallel group randomized controlled trials (RCTs) to individual patients [1]. However, many RCTs demonstrate a high heterogeneity of response, limiting the ability of clinicians to personalize therapy [2]. N-of-1 trials are a technique employing many of the same elements as classical RCTs, but focused on characterizing the response of a single patient.

Despite early successes and the promise of improved care and reduced costs [3], n-of-1 trials have not been adopted for broader use. This chapter describes how a modern information technology (IT) infrastructure and design approach can reduce the costs, burden to end users (patients and their clinicians), and complexity of administering and running n-of-1 trials at scale by automating trial workflow. IT infrastructure also represent new opportunities such as the ability to pull data from electronic medical records, integrate with emerging consumer health devices, regularly interact with patients or collect data via mobile platforms, and embed statistical analysis and visualization directly into web-enabled platforms.

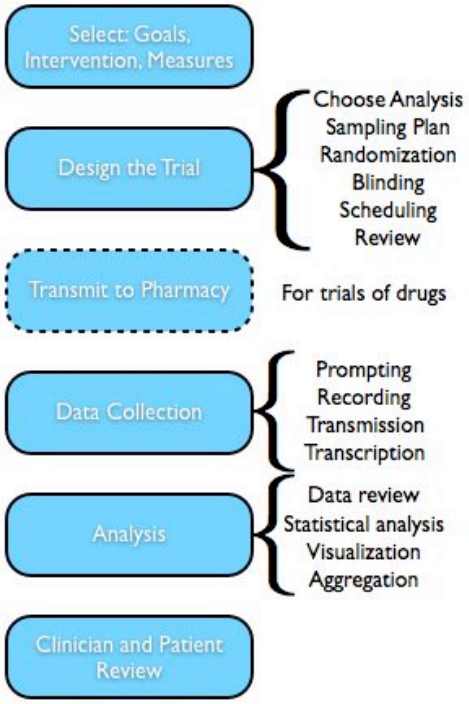


Figure 1 - Trial Workflow

Prior work addresses the procedures necessary to run individual trials using pen-and-paper techniques or simple electronic tools such as a spreadsheet [4]. None of the reported trial services has survived over the long term, in

part due the cost and complexity of running trials. In one system, the time spent per trial was approximately 16.75 hours. Of this ½ of the time was spent in setup and another 1/3 for trial execution [4]. Some of these time costs were attributable to carrying out the fundamental n-of-1 process, involving direct patient education and discussion. The remaining time was spent on activities related to trial design, transmission of design to the pharmacist, analysis, preparation, or presentation of results. A detailed discussion of costs can be found in Chapter 3 of this monograph.

Existing clinical trial management systems are inadequate for managing n-of-1 trials and are difficult to extend for this purpose. This chapter introduces features of an IT-based trial platform that will enable efficient scaling beyond individual provider use. It is written to provide clinicians, health services researchers, and IT specialists a shared framework for discussing the use of IT to support n-of-1 trials. It defines relevant terms, identifies key requirements of n-of-1 trial systems, introduces tradeoffs to be considered, and warns of common pitfalls to avoid. While all of the proposed features should be considered during a project's design phase, only a subset of the features are likely to be implemented in any one platform.

What is an N-of-1 Trial Platform?

A general trials administration platform facilitates all phases of design, execution, and analysis activity as illustrated in Figure 1. As compared to traditional trials, n-of-1 trials allow for greater patient participation in the selection and design phases through a dialog between a health professional and a patient and/or family member.

The design of the n-of-1 trial itself may be specified by the care provider independently, as a shared decision making exercise with the patient (e.g., choosing the interventions to compare, or the outcomes to track), or a patient driven process with provider review. In all

cases, IT can support these steps by providing ready access to standard libraries of characterized interventions, outcome measures, and statistical tools. IT can help clinicians and patients jointly explore tradeoffs that affect the time, strength, and overall burden of the trial.

The end result of the design phase is a schedule of phases with specified interventions and measurements necessary to execute the trial. An electronic platform can facilitate the trial's execution through data collection, treatment reminders, and pharmacy interaction where necessary. Some trials may involve action plans that accommodate real-world challenges such as acute sickness, changes in routine, or periods of non-adherence. The platform should support a variety of adjustments to trials and track these adjustments for use in a subsequent analysis.

When the trial is complete, the platform should execute statistical analyses as specified in the protocol, and the results be displayed for clinician interpretation. Presentation to patients should be performed in a shared decision making context. Proper visualization techniques backed up by statistical analysis are critical to facilitating interpretation of data collected in n-of-1 trials. Nearly all n-of-1 trials are conducted to inform a treatment decision in the ongoing care of a patient, therefore producing visualizations and reports that are accessible to end users (patients and their clinicians) is important. Shared decision making aids may also be an important part of facilitating the use of n-of-1 trials in clinical care.

At scale, many individual trials are likely to be variations on a common theme. A library of experimental designs should also be supported by the platform. Aggregated outcomes of prior trials of a design inform future users of potential problems with the protocol, such as inadequate power, and the prevalence of success across a population. Providers using the same protocol can exchange notes on or off of the platform. A scientific review process

could be built on top of this IT infrastructure to ensure that the methodology and analysis of each newly submitted trial are sound.

Implementation Feature Overview

We advocate a modular and extensible architecture be used in the design of n-of-1 trial platforms **(ref – OMH [5])**. In this spirit, we introduce a list of desired capabilities of a trial platform (Box 1), as a guide to evaluating a proposed approach to n-of-1 automation, or as a jumping-off point for designing a new approach.

Box 1 – Requirements of n-of-1 trial platform

Support for n-of-1 trials
- Record clinician and patient goals, experiment hypothesis
- Informed consent documentation
- Protocol Implementation Support
  - Library of characterized interventions (including details of onset, carryover, etc.)
  - Library of characterized measures (including precision and variance)
  - Support for randomization
  - Web service connections to acquire/share libraries of standard measures
- Trial Protocol Specification
  - Choice of Characterized Treatments
  - Choice of Measures
  - Choice of outcome variables and measures
  - Choice of length and number of intervention periods
  - Decide on important covariates to track
  - Analytical design
- Connection to EMRs, PHRs, pharmacies (obtain medication context, lab values, etc.)
- Data Collection and User Engagement Support
  - Data capture modules (e.g., choice lists, visual analog scales)
  - APIs to 3rd party data services such as sensors, apps (e.g., for symptom tracking)
  - Direct E-mail or SMS submission of Patient Reported Outcomes (PRO)
  - Trial progress review screens (for patients and clinicians), and other user engagement modules (e.g., leaderboards, rewards)
- Data Analysis and Review
  - Data pre-processing modules
  - Statistical analysis modules
  - Visualization modules
  - Data review and decision support modules

Institutional Support for n-of-1 trials
- Recruitment support
- Eligibility screening
- Informed consent / documentation
- Population review
- Summary reports (e.g., participation, utilization)

Aggregation of n-of-1 trial results
- De-identification of patient record
- Statistical analysis and aggregation of raw individual patient-level data
- Statistical analysis and aggregation of summary results data
- Statistical analysis and modeling of aggregated outcomes
- Models for using aggregated group outcomes to estimate individual-level heterogeneity of treatment effect

IT Infrastructure
- Secure data storage
- Data transmission security
- Data downloading
- Authorization controls (who can do what)
- De-identified views of data
- Auditing (who accessed what/when)

Regulatory Issues
- Written data governance policies (for IRB and HIPPA regulations)
- E-consent mechanisms

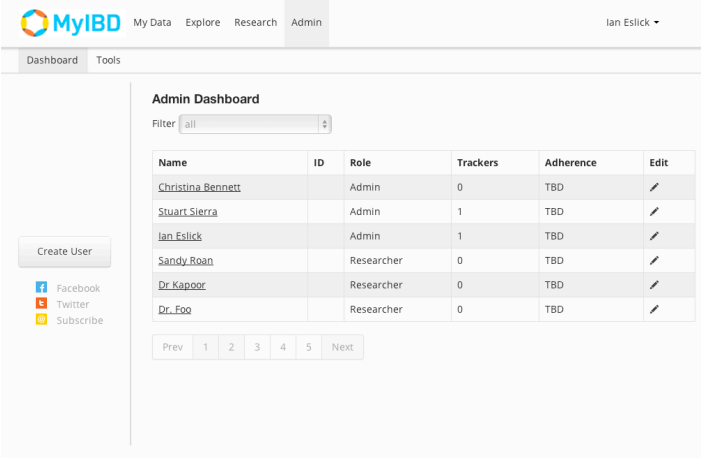
Source: http://www.effectivehealthcare.ahrq.gov/index.cfm

An n-of-1 trial platform will also need to support a wide variety of user roles at different stages of the process with different access to information maintained by the platform. Not

Patient and/or Caregiver	May access own data. Co-design n-of-1 trial. Enter data via web, sms, mobile app, device, 3rd party service. View and interpret results.
Clinician	Co-design n-of-1 trial, manages a small subsample of patients. Regular review of data. View and interpret results.
Administrator	Institutional oversight, user account creation and management.
Pharmacist	Receives instructions for specific patients/trials including randomization schedule and blinding requirements. May not need an account on the trial system (fax / secure e-mail data)
Statistician / Researcher	Reviews trial design and collected data for validity and/or aggregate analysis. May download identified or de-identified data for offline analysis
Systems administrator	Supports operation of the IT system, provides user tech support
Developer	Ensures operational code

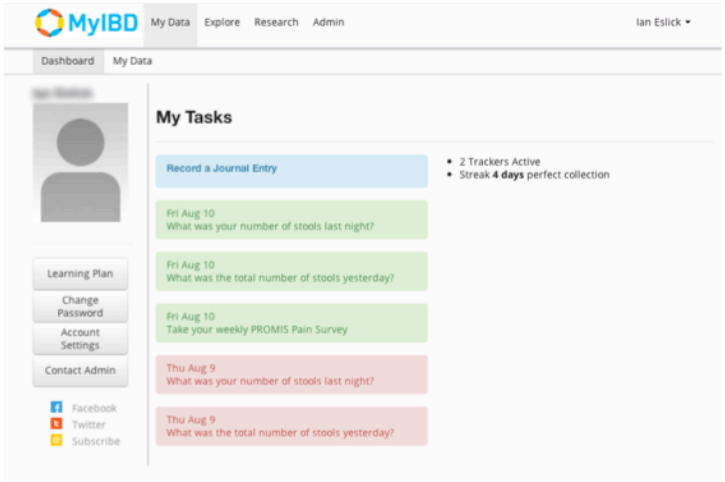
all technical platforms need implement all roles directly.

Example System: MyIBD

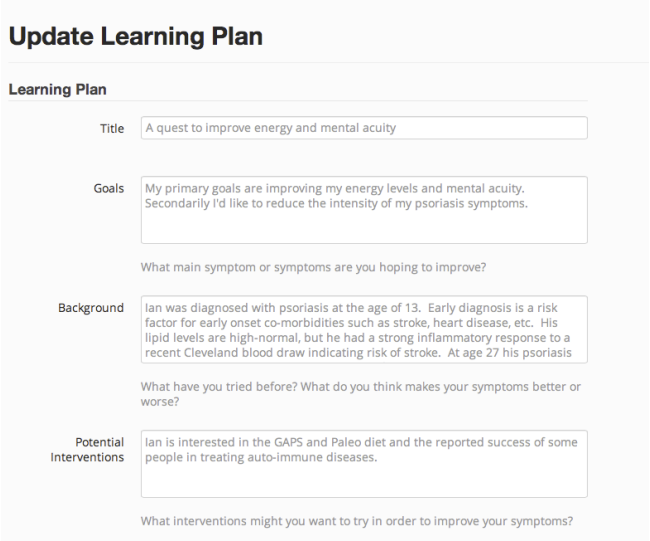


The MyIBD [6] IT platform was built for the Cincinnati Children's Hospital and Medical Center (CCHMC) as part of its Collaborative Chronic Care Network (C3N) health services research project. The system was constructed by a 3rd party consulting group (including author Eslick) that worked closely with the Cincinnati team to identify a minimal set of requirements to facilitate defining and

managing 100 concurrent, independently designed n-of-1 trials. The platform is part of a Personalized Learning System intended to more directly engage patients in evaluating treatments they try at home for which minimal research literature exists, as well as validating the individual efficacy of treatments with known heterogeneity of response. A web form is used to capture the trial goals and design constraints. The system supports simple A-B treatment responses as well as multi-phase withdraw/reversal or alternating designs. Trial outcomes are monitored using Shewhart-style statistical control charts.



The system supports three roles: Administrator, Researcher, and Patient. A Clinician role linked to a subset of patients with clinician population management features is planned. The service consists of a simple administrative dashboard to create and review user accounts. Administrators are the only users able to see patient identifiers. Researchers are shown a de-identified view of the active patients and can review any of the trials ongoing in the system.



Users are given a dashboard showing outstanding data recording actions, recently recorded data and additional views for configuring 3rd party services, updating data recording schedules, and a generic journal entry facility. Because of challenges integrating with the hospital's commercial EMR and network registry, manual entry of medication and treatment periods is facilitated via the Journal entry mechanism.

The initial target population is pediatric patients with an inflammatory bowel disease such as Crohn's and Ulcerative Colitis. An integration of three standard measures is provided including the PROMIS Fatigue (weekly), PROMIS Pain (weekly), and PEDS QL (monthly).

The clinical team opted not to support treatment blinding at the time of this writing. All of the collected data and treatment context is available to both patients and clinicians throughout the trial. A single data review screen currently provides a scrollable view of all measures. The measures are plotted on an Xbar control chart using 3-sigma control lines calculated from the first 20 measured data points (the minimal baseline period for this platform).

The full development costs for this system are anticipated to be over $250,000. The ongoing infrastructure and maintenance costs are currently $400/mo. This fee includes software and service licenses and a set of 4 cloud-hosted servers supporting redundancy, backups, SMS transaction fees and other miscellaneous costs. Additionally, a $1000/month support

contract was in place for the first year to secure 1-2 days/month of consultant time for critical bug fixes and small feature enhancements. The project is exploring making the existing functionality more widely useable, including a fee-for-service offering and open-source licensing of the underlying code base.

The benefit of this large up-front investment is that sustaining and per-patient costs are minimized, requiring only a small per-user fee. A single installation of the MyIBD platform is expected to scale to thousands of patients with only minor changes to the user interface. Scaling can also be accomplished through configuring the service on separate servers. The incremental per-user cost in the current system are almost entirely driven by usage fees for the SMS gateway service. Tracking 3 daily values per patient requires approximately 90 messages/month. At one cent per message and with thousands of total users, the amortized IT cost per user per month is estimated to be less than $1.00.

Design Considerations

The following sections take a deeper look into many of the important components of a trial platform listed in Box 1 and discussed above. We address here some of the tradeoffs and pitfalls that may be involved in these specific features to help evaluate a specific system or cost proposal.

N-of-1 trials rely on two critical components to ensure validity of the outcome: protocol-defined, time-varying exposure and systematic measurement.

Time Varying Exposure

Time-varying exposure refers to the restriction of patient behavior at different points in time to ensure they are exposed to the chosen treatment and to non-treatment, placebo or

alternative treatments according to a pre-specified schedule. The schedule of exposure needs to account for the operating characteristics of the treatment such as onset time, washout (for withdraw/alternating designs) and the variability of the measurement (how many samples are needed over what amount of time to get an accurate estimate of the outcome). All the issues involved in medication adherence are accentuated in n-of-1 trials due to the complexity of scheduled switches between interventions being tested. Simplifying treatment adherence using drugs or supplements may be facilitated via pre-packaged treatment intervals at a pharmacy [7] and/or automated reminders of what behavior is needed at a point in time.

An IT platform should accommodate the effects of unanticipated events (such as hospitalization, vacations, non-adherence) by allowing the study protocol to be adjusted or restarted mid-stream. For example, data collection may need to be suspended for a period of time, or phases of the trial may need to be restarted, possibly including re-verification of the patient's baseline. Changes may need to be made in trial execution (e.g., producing reminders, interacting with a pharmacy) or in analysis. This highlights the difference between an intended, "planned study protocol" and the actual "executed study protocol" (chapter)[8]. Accomplishing fully or partially automatic adjustments requires that the system have a representation of treatment effects such as onset and washout periods or facilitate explicit change of the schedule by an expert.

Measurement

The second critical component of an experiment is the measurement of observations of the patient over time. In published n-of-1 trials, measurements often consist of questionnaire responses or lab values at the end of a trial phase; however, n-of-1 trials are increasingly

leveraging time-series data, especially with mobile technologies that enable frequent "ecological momentary assessments"[9] (EMA) of patient symptoms. Time series data involve repeated daily or weekly measurements that are taken within a given phase of a trial. Each measurement may be a single value such as weight or a compound multi-dimensional assessment, e.g.,:

- **Timepoint or time unit**: e.g., length of time since start of an intervention, or a time frame of validity (e.g., over the last week)
- **Value(s)** (integer, decimal, categorical, ordinal, free text, compound, complex)
  - Devices often generate multiple and compound measures for a single time point (e.g. systolic and diastolic blood pressures or GPS latitude/longitude)
  - Complex responses include surveys[10] that can be summarized with a single value
- **Definition**: what does this value measure? Often this includes binding to a terminology or coding system, (e.g., LNC 1558-6, the LOINC code for fasting blood glucose), which is particularly important for aggregating data across multiple trials and/or centers

In any trial, but especially in n-of-1 trials, individual patient context may have a large effect on observed values and on overall trial results. For example, if a patient records a pain score of "2 at 10:30am EST on Tuesday, March 5th, 2013", we may also want to know:

- **Origin**. How they recorded the information. Was it via web, SMS, web application, a device, or paper?

- **Time recorded.** When did they record the value? They may have forgotten to record that morning and instead recorded it that evening, e.g. reporting at 10pm a pain score that was actually experienced at 2pm.
- **Prompt.** What, if any, prompt elicited the value?
- **Schedule.** What was the scheduling on this prompt? (Momentary assessment, or scheduled?) Randomization of prompts may improve the accuracy of the resulting data **(ref)**.
- **History.** Was the data ever changed or updated?
- **Originator.** Was the data entered by the patient or by a proxy (e.g. parent, caretaker)?

These "data about data" are called metadata. It is critical that a trial IT platform have robust support for collecting and storing metadata, because ancillary factors can interact with time series data. For trials with small effects or weak power (e.g., because of limited numbers of within subject comparisons), these interaction effects may overwhelm and mask the underlying effect of interest. Metadata are particularly critical when data from individual trials are aggregated to estimate population effects or to predict the likely outcome of future n-of-1 trials.

Templates and Libraries

As described above, a library of interventions and measures will help to simplify the process of trial design and specification, to increase methodological strength, and to enhance user engagement. Designers of n-of-1 trials can go to such a library to find detailed information about interventions, including their speed of onset, washout periods, and other factors that must be known to design a proper n-of-1 trial. Detailed information on outcome measures would also be helpful. Measurements have statistical properties that can be characterized

for the average respondent, such as reliability, variance, and reproducibility. Measurements may also be subject to biases, including practice effects, onset behavior, etc. These characteristics of interventions and measures must be taken into account to ensure methodologically strong scheduling and analysis of a specific trial.

An n-of-1 methodology library should also include parameterized templates of successful trials that can be used or adapted "off the shelf" by other patients with similar study questions. This will reduce the barrier for clinicians and patients who do not have the statistical or methodological expertise to design trials on their own to still be able to run n-of-1 trials. Classes of trials that have been successfully reviewed by statisticians and methodologists may be fully automatable, reducing overall personnel costs and burden, while increasing the methodological quality of executed studies.

A methodology library as we discuss here can be a component of a full-featured n-of-1 IT platform, or it could be a common shared resource. The closer such a library is integrated to an operational IT platform, the more that intervention and outcome measure characteristics could be populated directly from the results of prior trials (e.g., the typical within-subject and across-subject variations of a measurement).

Data Processing Modules

Chapter 4 identifies a variety of options for performing statistical analysis of n-of-1 trials which may include simple statistical tests of the properties of the different arms of a trial (t-test, ANOVA, etc.) or more sophisticated Bayesian analysis involving one or more types of priors using closed form or MCMC-based techniques for evaluation. Algorithmic support may also be helpful for filling in missing data, adjusting for time series effects (e.g. ARIMA

models), removing short-term special cause variations and pre-processing the data for visualization. Over time, different measures and different trial conditions may require new forms of analysis.

Most algorithms produced in the academic literature are implemented in a statistical language such as R or Matlab, thus export procedures for analyzing the data in external packages can be helpful. R, for example, can be embedded or linked as a web service to other software and that may simplify the creation and extension of the mathematical facilities of the trial platform. Extension of the mathematical facilities may become especially important if aggregation techniques are added to the platform over time as this is likely to be an active area of research in the coming years.

Visualization Modules

Many n-of-1 trials have strong effects, making it straightforward to analyze the trial outcomes using simple visual techniques. Visualizations typically involve a data preparation phase (data transformation, filtering, etc.), a customization of the data presentation (colors, emphasis, and labeling), and a rendering phase. If the trial platform is web-based, there are many off-the-shelf charting packages that may suffice, but for implementing the annotations that are often helpful to interpreting n-of-1 trial results, a more flexible graphics language such as D3 may be a more appropriate foundation.

Many clinicians and most patients have limited statistical numeracy[11]. N-of-1 trials therefore require very clear communication of trial results that use visual heuristics and offers, but does not require, statistical understanding.

Health IT systems are typically designed for clinical settings and often lack effective interaction design[12] (i.e., the visual and procedural experience of using a piece of software). Designing and implementing user interfaces is expensive, but building a seamless and engaging user experience can be an order of magnitude more expensive and challenging. With increasingly sophisticated user experiences becoming commonplace in consumer software (e.g., Apple iPhone), many patients and clinicians will expect equally sophisticated design from health IT. Thus, IT platforms designed to scale n-of-1 trials must devote adequate resources to user interaction design to ensure user uptake and engagement.

Extensibility

N-of-1 trials are an old technique, but remain novel to most health settings and have received limited attention from the academic research community. Techniques and trial design styles are likely to evolve and it is prudent for trial platform designers to adopt a modular, and extensible, approach to facilitate the adoption of new techniques over time. Ideally, extensibility is made possible through a "plug-in" architecture, allowing 3rd parties to add functionality to a well-defined application programmer interface (API) or data format without requiring a deeper understanding of the platform.

The areas most important to emphasize extensibility include: the component and template catalog, survey and prompt user interfaces (e.g. may want to incorporate new adaptive assessment models), processing modules, visualization modules, and shared-decision support.

The Open mHealth[13] standard identifies a data interoperability standard for storage and transmission of data congruent with this perspective along with a specification for

measures. It defines a framework for modular assembly of data processing and visualization modules to create specific time-based or summary views of time-series data.

Another model to consider is the Substitutable Medical Apps Reusable Technologies (SMART) platform[14], a standard that defines a model for pluggable applications for electronic medical record systems. SMART defines a web-based model for interoperability allowing 3rd party web-based user interfaces to plug into the patient portal of an electronic medical record or personal health record. Providing similar facilities would allow new developers to build shared-decision support screens, web-based instrumentation, or new visualization and/or processing solutions for a core platform.

Cross-cutting concerns

Underserved Populations

Technology promises to help close health disparities (ref, AHRQ had a recent one), but underserved populations have special needs that require special attention. The user interaction design should be culturally sensitive. Instructions and prompts should be expertly translated. Section 503 compliance[15] should also be sought if the targeted audience includes the visually or hearing impaired.

Privacy

An n-of-1 trial platform needs to be designed with the same consideration given to any health IT system that maintains patient data. The goal is to facilitate patient access, clinician utility, and 3rd party review with minimal effort, while preserving privacy consonant with ethical principles and applicable regulations. De-identification of data can provide partial privacy protection sufficient to enable authorized people to review records and explore aggregate data analysis safely and ethically. However, some types of data (e.g.,

location traces, genomic data) are almost impossible to de-identify. Privacy is best maintained and assured by a combination of technology and policy.

In US-based settings where research is performed on the data collected by the platform, all developers and system administrators will need to complete Human Subjects Training as they will have physical access to patient identifiers. (See Chapter 2 for a more complete treatment of human subjects issues relevant to n-of-1 trials.)

Security and HIPPA/HITECH

All US-based systems must guarantee that Protected Health Information (PHI) are encrypted "at rest" and "in transit". This means that data stored on the platform servers, or in backup archives, must not be directly readable. Data that is transmitted between components of the platform (such as web server and database, or between web servers and clients such as web browsers) must also be encrypted. Further, all procedures for managing access to data and system administration must be formally documented.

These issues may become particularly thorny in the interaction between a trial platform and 3rd party service. Standard SMS, for example, is not a secured channel and the patient's phone number is a piece of PHI. It is unclear at the time of this writing whether SMS is an acceptable channel for communicating with patients as part of ordinary care interactions. Under explicit research consent, it may be. The same holds true for consumer devices and services such as Fitbit[16] and FitnessKeeper[17] that collect and store consumer data on systems that may or may not be HIPPA compliant.

Legislation around the management of PHI will likely evolve during and after publication of this document. It is important to designate someone in the provider organization, even if outsourcing to a 3rd party, who can review the organization's obligations under current legislation with regard to documentation and notification in the event of a breach. They should audit the platform procedures prior to major updates and on an annual basis.

Authentication and Authorization

One critical consideration for platforms that expose interfaces to users (clinicians, patients, or any other user) is how those users will be authenticated to the system. Authentication is is the process of determining whether someone or something is who they say they are and authorization is the logic that determines what a given person can do. N-of-1 systems are particularly amenable to role-based authorization, where a given user satisfies one or more roles that in turn dictate what views or data they have access to. For example, clinicians can only review their own patients and reviewers can only see de-identified population and record review.

Everyone faces the problem of having to remember passwords for a wide variety of systems. An n-of-1 platform should seek to integrate where possible with existing authentication systems to facilitate easy credential recovery according to industry best practices.

Platform Economics

When considering buying or building an n-of-1 platform, the total cost of ownership should be carefully analyzed. The initial development of a trial platform may be a fixed cost and born by a research grant or one-time funds, but ongoing support costs, particularly as needs evolve, can be substantial. Resources will be required for ongoing user support, technical

support, hosting costs, and new feature development. Translation costs for multi-lingual support can be significant up-front but also over time as site content is updated. Service costs can be significant if users are contracting with 3rd party services such as an SMS gateway for eliciting data via SMS, telecom costs for phone/fax, and transcription costs for manually transcribing paper responses. Institutional owners of n-of-1 platforms may consider recharge mechanisms for defraying carrying costs.

Summary

Development of a custom IT-based n-of-1 trial platform requires significant up-front investment, as illustrated by the MyIBD example. Moreover, it will require significant ongoing investment for both operations and IT. Given the high costs ,the lack of strong evidence establishing value, and the small market, there are currently no commercially available n-of-1 trial platforms. It is likely that these platforms will be developed instead with government or foundation funding seeking to characterize the applicability and use of n-of-1 trials at scale.

Institutions interested in IT support for n-of-1 trials will find it prudent to maximize knowledge transfer and to amortize investments across multiple institutions by leveraging existing open source projects such as MyIBD. If in-house development and management of a clinical trials platform is impractical, it may be possible to use one of these open source platforms through collaborations with other institutions that are hosting those platforms.

Another option is to investigate reuse or extension of existing clinical trial management or other data acquisition systems, although many clinical trial management systems are designed explicitly for traditional randomized trials. In time, there may be commercial

service and/or software offerings that will provide lower cost of ownership and increased functionality to contrast with open source alternatives.

It is possible to facilitate many of the n-of-1 trial activities without the comprehensive design approach advocated here. MyIBD provides one example of simplifying and accelerating n-of-1 trial deployment with only a small subset of these features. However, each of the features advocated here will expand the population a platform can serve with improved ease-of-use and reduced costs.

Checklist: N-of-1 Trial Platform selection and deployment strategy

Guidance	Key Considerations	Check
Determine the purpose for which you are creating or buying an n-of-1 trial platform	- Recommendations depend on purpose. - Common purposes include: improving care delivery, evaluation of benefit, enable HSR, evaluate specific methodologies, generate reusable knowledge, integrate with a larger learning system.	☐
Decide whether to build or buy	- Perform an assessment of lifetime costs - Account for training, education, user support, statistical consultant and technical support costs. - Account for future needs and access to developers if developing or using open source offerings - Build only if you are performing research on trial design, statistics, or implementation AND have access to a captive development team. - Buy if you are able - Avoid using 3rd party contractors on one-time research-funded contracts	☐
Decide on open or closed source solutions.	- Use open source if you plan to innovate on the platform itself. - Prefer open source, but choose the best solution if your goals are improving clinical care delivery.	☐
Choose a hosting model. Is the service hosted in your institution's facility, or managed by external resources on servers not under your direct control?	A cloud solution is preferred if it satisfies your institution's HIPPA and/or IRB obligations and integrates with your clinical systems where needed.	☐
Define patient ownership of and access to data	- Patient should have direct access to their raw data after a trial is completed - Ideally, provide a patient portal for access during and after the trial with user-appropriate visualizations. - Support data download using standards like Open mHealth, BlueButton, and/or simple comma-separated values (CSV) - Provide an API to enable 3rd party services to pull data on behalf of users, e.g. via Oauth	☐

Checklist: Feature Requirements of an N-of-1 Trial Platform

Guidance	Key Considerations	Check
Assure that platform is sufficiently flexible to support the range of anticipated n-of-1 designs	- Involve methodologists and statisticians in developing the design specifications of the system	☐
Protocol design support	- Support a catalog of treatments, measures, and experiments - Support user interface workflow to create new measures, treatments, and experiments. - Ensure the platform supports all your likely trial designs (randomized, counterbalanced, blocked, etc.). - Platform should allow for designs to be extended over time (via a modular design)	☐
Provide a population management view	- Support de-identified access to trial cases for statistical review - Support configurable blinding of investigator and patient accounts	☐
Adaptive schedule management	- Enable users/clinicians to restart trial phases, annotate special causes, etc. - Allow for patient-driven selection of data collection prompts and/or reminders	☐
Provide a web-based portal for trial review by all participants	- Provide a portal for review of all filtered trials including summaries of progress, adherence, and any electronic conversations - Provide integrated methods for patient contact - Provide visualizations of outcome data after any blinding periods have expired	☐
Provide built-in data collection facilities	- Provide built-in assessment tools for common measures available via prompts, web survey tools, e-mail, and paper - Provide standard instruments, where possible	☐
Support download of trial data for post-trial analysis	- Allow for de-identified download of raw data for additional statistical review in case platform analysis is insufficient for a specific trial	☐
Obtain requisite data from the Electronic Medical Record	- Integrate with the medical record to populate contextual information including medication, and demographic information - Provide automatic access to lab results - Optionally, provide support for manual entry and display of this information alongside trial results	☐
Enable connection to pharmacist services	- For platforms testing drugs, provide support for printed, e-fax, and e-mail of pharmacy instructions - Instructions should include support for randomization schedules, blinding, and placebos.	☐

Checklist: Optional Features of an N-of-1 Trial Platform

Guidance	Key Considerations	Check
Provide multi-lingual and culturally sensitive versions	- Must support if deployment is anticipated with multi-lingual and/or culturally diverse populations. - Translations of common measures, reminder prompts, etc. should be shared in common libraries.	☐
Ensure Section 508 compliance if applicable	- Depending on the anticipated patient population, accommodation for patients and clinicians with auditory, visual, and physical disabilities is needed. - Government agencies are subject to Section 508 (29 U.S.C. 794d)	☐
Integration with other institutional IT systems	- Support external authentication schemes to reuse existing credentials e.g. from patient portals - Optional. User interface embedded (via iFrame) into institutional portals or intranets.	☐
Provide printed forms and reports; support manual transcription from paper.	- Expands the reach of the platform to underserved populations or populations without connectivity. - Enables consistent data capture when electronic systems are unavailable or inaccessible for any reason.	☐
Support scanning of printed records	- Optional. Support for Scanning and/or OCR of paper records will reduce workflow costs and enable de-identified transcription.	☐
Interoperate with 3rd party services	- Provide support for importing data from mobile devices, medical and consumer devices, and 3rd party service platforms	☐

Checklist: Additional Considerations for an N-of-1 Trial Service

Guidance	Key Considerations	Check
Provide education materials.	- Platforms should provide support for educational materials and aids embedded in the IT infrastructure. - Provide support for developing and maintaining culturally-relevant translations of educational content as required to serve the target population..	☐
Simplify human subjects research	- Support e-consent procedures - Support unique ID generation or import of unique IDs generated elsewhere	☐
Simplify methodology review	- Provide facilities for online and offline methodology review	☐
Provide user support	- Ensure that a nurse practitioner or the equivalent with N-of-1 trial experience can respond to questions such as what to do about missed treatment, lost data entry, and medication side effects - Optional. Provide an integrated live chat feature in the patient portal.	☐
Provide technical support	- Provide a telephone number to call for technical support and e-mail address with turnaround guarantee - Technical support should include a formal issue tracking system	☐

Bibliography:

1. Fletcher R, Fletcher S, Wagner E. Clinical Epidemiology: The Essentials. 3rd ed: Williams & Wilkins; 1996.
2. Furberg C. To whom do the research findings apply? 2002;87.
3. Scuffham PA, Nikles J, Mitchell GK, Yelland MJ, Vine N, Poulos CJ, Pillans PI, Bashford G, del Mar C, Schluter PJ, Glasziou P. Using N-of-1 Trials to Improve Patient Management and Save Costs. Journal of General Internal Medicine. 2010;25(9):906-913.
4. Larson EB, Ellsworth AJ, Oas J. Randomized Clinical-Trials in Single Patients during a 2-Year Period. Journal of the American Medical Association. 1993;270(22):2708-2712.
5. Chen CN, Haddad D, Selsky J, Hoffman JE, Kravitz RL, Estrin DE, Sim I. Making Sense of Mobile Health Data: An Open Architecture to Improve Individual- and Population-Level Health. Journal of Medical Internet Research. Jul-Aug 2012;14(4):126-134.
6. Eslick I, Kaplan H, Chaffins J, Margolis P. MyIBD. 2012; https://myibd.c3nproject.org/about.
7. Guyatt G, Sackett D, Adachi J, Roberts R, Chong J, Rosenbloom D, Keller J. A clinician's guide for conducting randomized trials in individual patients. CMAJ. Sep 15 1988;139(6):497-503.
8. Sim I, J. N. Eligibility and Protocol Representation. 2012.
9. Shiffman S, Stone A, Hufford MR. Ecological momentary assessment. Annual Review of Clinical Psychology. 2008.
10. David C, Susan Y, Nan R, Richard G, Karon C, Bryce R, Deborah A, James F, Bonnie B, Mattias R. The Patient-Reported Outcomes Measurement Information System (PROMIS). NIH Public Access. 2010.
11. Gigerenzer G, Gaissmaier W, Kurz-Milcke E, Schwartz LM, Woloshin S. Helping Doctors and Patients Make Sense of Health Statistics. Psychological Science in the Public Interest. 2008:53-96.
12. Cooper A, Reimann R, Cronin D. About face 3: the essentials of interaction design. 2012.
13. Estrin D, Sim I. Health care delivery. Open mHealth architecture: an engine for health care innovation. Science. 2010;330(6005):759-760.
14. Mandl KD, Mandel JC, Murphy SN, Bernstam EV, Ramoni RL, Kreda DA, McCoy JM, Adida B, Kohane IS. The SMART Platform: early experience enabling substitutable applications for electronic health records. Journal of the American Medical Informatics Association. Jul 2012;19(4):597-603.
15. Programs OoFCC. Section 503 of the Rehabilitation Act of 1973, as amended. 1993; http://www.dol.gov/ofccp/regs/compliance/sec503.htm.
16. Fitbit, Incorporated. Fit Bit. 2013; http://www.fitbit.com/company.
17. Fitness Keeper, Inc. 2013; http://runkeeper.com.