INTRODUCTION

Currently, the clinical trial enterprise functions largely independently from the clinical practice setting. Embedding trial elements into clinical practice can enable evidence-based quality care and reduce clinical trial inefficiencies. While we can learn from and repurpose examples of embedded interventional trials, as a united health care front we need to work together to drive change and reduce cultural, administrative, financial, and data-related barriers.

To accomplish this, CTTI carried out qualitative, in-depth interviews with sponsors and with those conducting interventional clinical trials that are embedded into clinical practice, and gathered input from a multi-stakeholder project team and Expert Meeting. The output was a set of recommendations, described below, to facilitate the integration of randomized, interventional trial elements* into clinical care.

Appreciating that the concept of embedding a trial is not all or nothing, benefits can be gained regardless of the degree of embedding or the number of elements that can be integrated into clinical practice. CTTI recognizes that limitations exist and that certain trials may have elements that are easier or harder to embed into specific clinical settings. For example, an open label cancer trial conducted in an academic medical center with assessments that are aligned with standard of care may be easier to embed trial elements than a blinded, investigational new drug study conducted in a community practice setting.

CTTI also acknowledges that the recommendations listed below may have financial implications. Our current clinical trial enterprise is inefficient and expensive and although embedding elements of clinical trials into clinical practice may increase some costs, it also has the potential to reduce costs. Despite questions that remain around financial accountability, progress is being made as seen with the Patient Protection and Affordable Care Act (ACA) and the CLINICAL TREATMENT Act, reimbursement policies that require insurance companies and Medicaid programs to cover routine costs associated with qualifying clinical trials.

These recommendations are intentionally focused on the operations of embedding elements of clinical trials in clinical practice. As with all clinical research, the protection of human participants is an important priority. Appropriate informed consent, IRB oversight, and other measures to protect human participants are as important for embedded trials as for any other clinical research. Because the primary objectives of clinical care (improving the health of an individual patient) and clinical research (developing new generalizable knowledge to improve the health of future patients) differ, it is important that clinical care providers involved with embedded clinical trials have appropriate organization, training, and oversight to protect the interests of their patients and the integrity of the clinical trials.

*Refer to page 4 for a table of example elements. Trials include, but are not limited to, global trials of drugs, devices, and biologics intended for regulatory review across the medical product review lifecycle.
Ultimately, by enabling health care systems to participate in embedded trials and assisting sponsors with their design and conduct, these recommendations aim to draw attention to areas where we can push the boundaries, identify future needs to encourage the further development of a learning health system, and improve clinical evidence generation.

### RECOMMENDATIONS SUMMARY

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Recommendations 1-7 are particularly relevant for: sponsors, clinicians interested in conducting research, CROs, funders, health care settings, technology providers, patients/caregivers/patient advocacy groups, payers, and regulatory bodies.

Recommendations 8 & 9 are particularly relevant for: health care system leaders, regulatory bodies, funders, patient advocacy groups, and policy makers.

Numbering of each recommendation is for identification purposes only and does not reflect a sequence.

### Embedded Clinical Trials Aim to Have:

- ✔ Elements integrated into health care delivery
- ✔ Accessibility to patients at the point of care
- ✔ Close alignment with clinical workflows
- ✔ Ability to use clinical care data sources for research purposes
# The Case for Embedding Clinical Trials into Clinical Practice

Care should inform research ↔ Research should inform care

<table>
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<tr>
<th>Patients</th>
<th>Providers</th>
<th>Sponsors &amp; Investigators</th>
<th>Regulators</th>
<th>Payers</th>
<th>Health system leaders</th>
</tr>
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<tr>
<td>Uses health care data for research to represent more real life experiences</td>
<td>Potential to engage in research with minimal burden</td>
<td>Generalizable research populations and evidence</td>
<td>Sufficiently sized trials with diverse populations</td>
<td>More, diverse data for reimbursement decisions</td>
<td>A means to innovate and support quality care</td>
</tr>
<tr>
<td>Less burden to participate in research</td>
<td>Address clinically meaningful questions to improve care in a broad population</td>
<td>Insight into real-world implementation of medical product interventions</td>
<td>Leverages power of randomization and RWD in the context of regulatory decision making</td>
<td>Better understanding of the effectiveness and safety of medical product interventions</td>
<td>Potential to attract new patients with research opportunities</td>
</tr>
<tr>
<td>Greater trial diversity and inclusivity</td>
<td>Treatment optionality for patients</td>
<td>Potential for increased efficiency and cost savings by reducing duplication of trial and care activities</td>
<td>Generalizable evidence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Recognize that embedding a trial into clinical practice is not all or nothing

Elements of a randomized trial can be integrated into health care delivery as suggested in the FDA RWE Framework, Trial Designs Using RWD to Generate Evidence section.\(^5\)

Trial designers should recognize that benefits can be gained regardless of the degree of embedding or the number of elements integrated into clinical practice.

The table below describes elements of a trial that can be embedded into clinical practice.

<table>
<thead>
<tr>
<th>Trial Element</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility Criteria &amp; Patient Identification</td>
<td>Identification and screening for participants can occur via an automated eligibility check (for some or all criteria) in the electronic health record (EHR) or registry. EHR information also can help provide data for power calculations. (See CTTI RWD recommendations for more information.)</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>As with all clinical research, appropriate informed consent and other measures to protect human participants are necessary. Patient portals and electronic consent can facilitate delivery of consent information via a variety of options and the consent process can be better integrated into clinical practice during in-person or virtual visits.</td>
</tr>
<tr>
<td>Randomization</td>
<td>An algorithm can be embedded in the EHR for individual-level randomization. (Other randomization approaches, as appropriate, may include cluster randomization or pulling curated data that can then be randomized to populate a study.)</td>
</tr>
<tr>
<td>Intervention</td>
<td>An interventional medical product can be embedded in the EHR to prescribe or not prescribe as part of routine care and/or can be distributed by local care facilities.</td>
</tr>
<tr>
<td>Trial Data Acquisition</td>
<td>Specific outcome assessments can be integrated into EHR data capture and/or research-specific outcomes can be modified to accommodate data capture in routine care (efficacy endpoints, safety monitoring, follow-up, including suspected adverse events and patient experience data). Existing data can also be used to auto-populate medical history and concomitant medication fields into clinical trial databases with the use of natural language processing (NLP) and/or tools that extract and curate data. Data collection can involve parsimonious trial data that is aligned with standard of care (e.g. EHRs, registries, and/or claims databases) or adjunct data collection involving non-standard data not routinely collected in existing data sources.</td>
</tr>
</tbody>
</table>
| Evidence Integration        | Data can inform care in an acute/short term way (e.g. results that inform adaptive randomization towards a beneficial therapy during an individual
trial) and/or in a long term way (e.g. final trial results contribute to a broader, more generalizable evidence base to inform clinical practice widely).

CTTI compiled 5 Case Examples that demonstrate, at a study level, how embedding trial elements has occurred in different settings. The table below provides a brief summary of those examples.

### CLINICAL TRIALS WITH EMBEDDED TRIAL ELEMENTS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Includes U.S. sites?</th>
<th>Regulatory review of a medical product?</th>
<th>Type of Medical Product</th>
<th>Investigational Medical Product included?</th>
<th>Embedded Trial Elements</th>
<th>Health Care Data Source(s)</th>
<th># of Participants (as of April 2022)</th>
<th># of Sites (as of April 2022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECOVERY</td>
<td>No</td>
<td>Yes</td>
<td>Drug, Biologic</td>
<td>Yes</td>
<td>Eligibility, Intervention, Data acquisition, Evidence Integration</td>
<td>National health care datasets</td>
<td>47,465</td>
<td>~200</td>
</tr>
<tr>
<td>I-SPY</td>
<td>Yes</td>
<td>Yes</td>
<td>Drug, Device, Biologic</td>
<td>Yes</td>
<td>Intervention, Data acquisition, Evidence Integration</td>
<td>EHR</td>
<td>2,000</td>
<td>30</td>
</tr>
<tr>
<td>VA Diuretic Comparison Project</td>
<td>Yes</td>
<td>No</td>
<td>Drug</td>
<td>No</td>
<td>Eligibility, Intervention, Data acquisition</td>
<td>National VA EHR, Medicare, NDI</td>
<td>13,523</td>
<td>72</td>
</tr>
<tr>
<td>TASTE (completed)</td>
<td>No</td>
<td>No</td>
<td>Device</td>
<td>No</td>
<td>Eligibility, Randomization, Data acquisition, Evidence Integration</td>
<td>National registry database</td>
<td>7,244</td>
<td>29</td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>Yes</td>
<td>Yes</td>
<td>Drug, Biologic</td>
<td>Yes</td>
<td>Eligibility, Intervention, Data acquisition, Evidence Integration</td>
<td>EHR</td>
<td>11,131</td>
<td>359</td>
</tr>
</tbody>
</table>
2. **Assess whether clinical trial elements should be embedded into clinical practice**

When determining whether to embed trial elements into practice, sponsors and health care systems should:

- Aim to lessen duplicate efforts already occurring in care while still answering the study question(s) with adequate scientific evidence.
- Realize that embedding elements of a trial into clinical practice should not jeopardize the protection of participants during the trial or the ability to obtain reliable results and meaningful information to answer the research question.
- Consider the research question and the ability and capacity of health systems to embed selected trial elements into clinical practice. (see tool below)

CTTI developed a survey to help trial designers and sites assess the feasibility and capability of embedding clinical trial elements into clinical practice and appreciate site readiness.

**Tool:** [Embedding Trials Feasibility Assessment Tool](https://ctti-clinicaltrials.org/our-work/novel-clinical-trial-designs/integrating-clinical-care/)

At a high level, trial designers and health care systems should consider embedding trial elements when:

- Patients and participating health care providers have provided input into research design and agree that the proposed, clinically-relevant endpoints offer clinicians an opportunity to improve their patients' outcomes and their own delivery of care.
- Logistics of trial implementation, including burden and time commitment for both participant and site staff, can be modified to integrate into clinical care workflow with adequate reimbursement for clinician time and participant expenses.
- The design can adequately address the research question and regulators, patients, and health care providers agree to the approach.
- The number and variation of data sources to be used are understood, as well as their capability to support research conduct.
- Data is able to be accessed, sorted, and extracted from existing data sources (e.g. EHR) for trial purposes.
  - Consider whether an informatics layer exists that can facilitate data aggregation across data sources (e.g. EHRs) or whether individual efforts with each data source is required.
- The processes used for embedding trial elements are conducive for future trials and not continually redeveloped for every embedded trial.
3. **Verify that data sources used for embedded trials are fit for purpose—relevant and reliable**

Clinical trialists and sponsors must understand 1) how the data are collected, 2) what issues commonly arise with that data, and 3) how data would be transferred to a research database. For strategies and supporting tools around data acquisition and assessing data fitness for use, see NIH Pragmatic Trials Collaboratory’s Data, Tools, and Conduct.

In addition, a number of EMA guidelines and FDA guidance documents exist to facilitate the use of real world data for regulatory decision making. Considerations specific to data relevance and reliability are listed below.

### Relevance (accuracy and intention)

- Use data collected during routine care delivery as the primary, foundational source data, when possible.
- Collect and curate only data necessary to characterize the trial population, answer the research question, and address longitudinal trial follow up.
- Collect supplemental data when those data are determined to be critically needed to meet the trial endpoints. If supplemental data is obtained remotely outside of the health care setting then the implementation and oversight obligation should not belong to the health care provider(s) but reside with the trial Sponsor, their agents (e.g. a CRO), or their solution provider contracted to provide this service.
- Appreciate the intention and potential consequences of clinical care data collection and use, as this may influence the level of data validation needed for trial purposes.
  
  *For example, data for safety and efficacy events typically require double-checking to ensure that the events of interest are fully captured, ascertained, and confirmed. For trials with real world data acquisition embedded, such as that captured during routine care delivery and/or from connected sensors like wearables, this data can be used for initial signal detection that then prompts supplemental data collection and centralized review to confirm or refute whether an efficacy or safety event has occurred.*
- Recognize that aligning research data with clinical practice may span the continuum of care and should be evaluated for changes over time and when routine care practices change.

### Reliability (data accrual and data assurance)

- Confirm with data experts across health care systems which clinical data fields are reliable and which are not, or how variations in clinical documentation in data systems (e.g., EHRs) across the health system may affect the reliability of the data. Appreciate the timeliness of the data entered into the clinical data source.
  
  *For example, claims data may be subject to a time lag to allow for adjudication of claims.*
- Develop strong data privacy and security plans, provenance, and methods to ensure that patient healthcare data collected and incorporated into the trial database are used...
responsibly, securely managed, and processed so as to minimize the risk of a data breach or other breach of patient confidentiality.

- Understand regulatory requirements on the use of computerized systems as source documents, specifically what systems need to be Part 11 validated and what systems do not.\textsuperscript{11, 12}

- Consult early and often with regulatory authorities on data relevance and reliability for trials that are intended to inform regulatory decision making. This may include consults with relevant review divisions at the FDA early in the planning of studies, (e.g. during a pre-IND meeting) and subsequently during the development of trial protocols.

### 4. Streamline trial design to align with clinical workflows

Embedding trials into complex health care delivery systems requires the trial’s design and operational conduct to be minimally disruptive and as streamlined as possible.

Sponsors and Clinical Research Organizations (CROs) should:

- Review the protocol and keep only those trial procedures and data collection that are both 1) essential to the trial objectives and 2) can be coordinated with routine care. All other procedures and data collection should be eliminated from the protocol unless strongly justified from a scientific and/or safety standpoint. See FDA’s [Real-World Data guidance](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data) for additional information.

- Limit the number and amount of data queries that are issued to trial sites to just those that are essential to confirm the validity of the key trial data elements, such as data related to efficacy and safety endpoints.

- Be flexible with respect to the equipment needed for the trial (e.g. blood pressure cuffs, EKG machines), the timing of visits and the procedures within those visits so that routine encounters can be leveraged as much as possible. If there is a discrepancy, decide if workflows can be adjusted for the trial or if embedding the trial is not a good fit for the setting.

- Facilitate repurposing of embedded trial processes by developing re-useable protocols that are adaptable for future studies, such as master protocol designs (for more information see CTTI’s [Master Protocol Studies](https://www.ctti-clinicaltrials.org/our-work/novel-clinical-trial-designs/integrating-clinical-care/) recommendations). Standardization of trial designs and processes across trials would prevent the need for expensive and inefficient individual level trial adaptations.

- Receive stakeholder input early in the design process. For more information, see Appendix 1 for a list of stakeholders to engage during study conception and protocol design.
OPERATIONAL RECOMMENDATIONS

5. Ensure site readiness to embed trial elements

Site readiness includes adequate staffing and technology resources for activities beyond routine care, such as Information Technology (IT) personnel to program trial elements into the EHR, site staff to ensure allocation of resources to implement the intervention, and appropriate resources for safety monitoring and reporting.

See CTTI’s Embedding Trials Feasibility Assessment Tool to appreciate site feasibility and capability to embed trial elements into clinical practice.

Sponsors and CRO’s should also work with sites/health care systems to:

- Align clinical trial oversight with the trial objectives and any inherent risks of the embedded trial elements.

- Appreciate what role each member of the clinical staff, if willing, can play in research activities.

- Evaluate what level of resources and degree of training various settings will require.

- Pro-actively train and support clinical staff to be fully informed of and ready to complete research-related tasks and requirements for embedded trials. (see CTTI’s Investigator Qualification recommendations)
  
  - Training should be role-based.
    
    For example, a floor nurse limited to providing an EKG may not need a complete GCP training course but should be able to demonstrate competency in EKG administration.

  - Training should be non-duplicative and the minimal necessary to ensure scientific integrity and patient safety.

    Specifically, a nurse already credentialed and privileged by a hospital to take blood pressure on a patient should not need to duplicate that training simply for the protocol unless there is a justifiable reason.

  - Training should be continuous, easy to complete, and incorporated into other ongoing professional education and training requirements of the site.

    Consider eLearning or dynamic learning.

- Ensure that ICH E6 and Good Clinical Practice (GCP) requirements for clinical staff and health care providers participating in embedded trials are not compromised when trial processes and procedures are fit into clinical care delivery workflows. In many cases, a centralized oversight model leveraging experienced research coordinators and clinical trial site investigators may be the most feasible solution.

- Consider use of a single IRB of record (sIRB) in the United States, and/or central country ethics committees outside of the U.S., to increase consistency and efficiency in the ethics review process. Ideally, the sIRB selected will have experience with reviewing trials.
embedded in healthcare and have relationships with many of the planned study sites (see CTTI’s sIRB recommendations).

- For late stage premarket development or during post-approval clinical investigations, select safety reporting requirements that address the most relevant and impactful potential safety hazards based on prior cumulative safety experience with the intervention to be tested. Additional information can be found in FDA’s Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations. For trials intended for regulatory review of a medical product, ensure that adverse event data is complete enough such that a satisfactory understanding of the reasonable risks of the medical product can be understood.

- Assess the sites current connections with the local community and help support efforts to engage community clinicians and build connections if gaps exist between the research site and the community it serves.¹³

- Facilitate ways to encourage research participants to provide important information including alerts of key events or safety concerns, such as reporting through a wearable or an app.

- Leverage technology where appropriate to enable and streamline integration of research into clinical practice.

  For example, automated routine surveillance of the EHR clinical database for safety events can streamline interactions with participants to lessen staff burden.

6. Minimize participation burden for participants, providers, and research staff

As noted above, embedding trials into complex health care delivery systems requires the trial’s operational conduct to be minimally disruptive and as streamlined as possible. For multi-site trials, workflow change, such as adjustments to a provider’s post-visit note taking, may be needed by some sites. Workflow change is no small task. To minimize trial participation burden on health care providers, research staff, patient participants and care partners, sponsors should:

- Communicate across health systems¹⁴ to determine how technology solutions can facilitate changes that meet both research and clinical needs.

- Invest in upfront planning to implement technology solutions.

- Work with IT experts in health care settings to automate what can be done before or during clinical care encounters, such as trial prompts and flags.

  E.g., alerting health care providers at the point of care through the EHR can identify potentially eligible trial participants.

- Provide and communicate the availability of research support staff so that health care providers feel supported and not overwhelmed.
  - As appropriate, consider using virtual patient contact and monitoring.
7. Validate the quality of the clinical data for research purposes

Through clinical staff training, sponsors and health care settings should ensure that clinical data incorporated into a trial database are complete, plausible, accurate, and have traceability, especially as data are transformed into the study dataset. To do so:

- Assess missing data as part of a feasibility assessment for a given embedded trial.

  *E.g., a trial that will rely on fields that are in the EHR should ensure that the fields are routinely completed by health care providers.*

- Perform periodic checks during the trial that focus upon comparing a subset of system-generated clinical data to a data set that was abstracted manually. Use existing tools to automate checks.

  *E.g., Observational Health Data Science and Information’s open-source data quality dashboard tests the quality of data from EHRs with structured query language (SQL) coding.*

- Consult with clinical and IT staff about potential quality issues related to data fields needed for trial purposes and pre-emptively address any issues identified.

- Collaborate with data technology experts to develop open-source algorithms that facilitate quality assurance checks of clinical data that are incorporated into trial databases (looking for outliers, improbable values, columns that don’t match, unit issues, etc.). The approaches should be repeatable to ensure widespread use and availability.

- Use data standards that have health care provider input and comply with health care data interoperability laws, such as US CORE data elements and Health Level 7 (HL7) international standards which can enable interoperable, two-way transferring and sharing of data between clinical care and an embedded clinical trial.

HEALTH CARE & RESEARCH CULTURE RECOMMENDATIONS

8. Recognize and invest in research activities

Integrating research into the health care provider’s day to day work can bring attention to research and its value but must be done in as minimally disruptive way as possible. Examples of how to encourage research and spread awareness without overburdening providers are provided below.

General Research Awareness and Support

To recognize and communicate the value of participation in clinical trials, health care system leaders should:

- Incorporate trials into clinical treatment pathways, and clinical decision support systems when appropriate, so that trials are considered an option when current best available clinical care is inadequate.
Credit the time health care staff spends on research recruiting, consenting, etc. towards their overall productivity assessment. Consider new compensation models like research RVUs.\textsuperscript{16}

Streamline contracting by encouraging master service agreements and master contracts between trial sponsors and health care systems so that individual trial contracts can be negotiated and executed as rapidly as possible.

Highlight and recognize research participation and opportunities in routine communications to all employees and patients (e.g., president or CEO newsletters, town halls, general staff meetings).

\textit{E.g., by noting how the institution has contributed to a trial’s findings and the consequence of participating, such as contributing to a new therapeutic option, improved outcomes, etc.}

Encourage frontline clinicians who work in underserved populations to conduct research. Trusted health care providers in trusted health care settings can encourage patient engagement and help enable equity in trials. Incorporate community outreach and engagement in trial conduct, working with trusted community members.

\textit{E.g., frontline clinicians may appreciate the opportunity to meet continuing education or academic credit through research or collaborative authorship.}

Ensure that leaders from informatics, health IT, data science, and information security groups understand the importance and prioritization of research participation and are appropriately motivated, compensated, and supported to realize these goals and to create cross functional collaborations.

Identify improvements in data infrastructure that serve both care improvement and clinical research.

**Individual Trial Awareness**

Health care systems should work with sponsors and investigators to develop plans to introduce research at various touchpoints, appreciating the patient and health care provider journey, and recognizing that the Institutional Review Board (IRB) will have input into the types of notification and authorization that are required.

Example ways to introduce research include:

- \textit{Physical notices of research options}, such as signage at doors and other transition points, flyers at reception desks and in patient rooms, and screensavers in waiting rooms.
- \textit{Digital notices of research options}, such as videos and secure messages in a patient portal, which can include information specific to a particular trial that a patient may qualify for.
- \textit{Research consent in routine care delivery}, such as during the clinical care appointment. To integrate consent, health care settings should:
  - Understand the workflow, who will be presenting the consent, and whether additional resources will be needed to facilitate this.
Communicate and obtain agreement with the sponsor if local healthcare providers are obtaining consent so the sponsor can provide necessary training.

Ensure that the treating health care provider knows who is being contacted about a trial.

To streamline consenting into the workflow, the sponsor can create a cover page with a short, plain language summary and incorporate multimedia approaches that can be used as discussion aids to facilitate understanding. E-consent is also possible, which can be interactive and involve short quizzes to ensure understanding and which comply with regulatory standards such as 21 CFR parts 11, 50, and 56, to facilitate consent outside of the limits of an office visit.

9. Promote the basis for and ways to embed trial elements into clinical practice

Embedding trial elements and developing a learning health care system is best accomplished in partnership with support from leadership across health care systems and the clinical trial enterprise (CTE). As such:

**Health care system leadership** should:

- Acknowledge that a stronger IT infrastructure has the potential to provide multiple benefits to patients and providers.
- Encourage building a digital infrastructure that can improve the usefulness of real-world data sources.
- Develop a financial framework to ensure that research resources and technology costs will be appropriately covered on a repeatable basis.
- Work with trial sponsors to develop communication plans.
- Encourage the development of quality improvement approaches across health care systems that emphasize and incentivize standardization for how clinical care data are captured, documented, and validated by clinical care staff.

**Large government and policy led forums** should:

- Promote and advance the rationale for embedded trials to improve evidence generation.
- Encourage regulatory, reimbursement, and policy changes.
- Develop consensus-driven data standards and acknowledge international opportunities to align standards.
- Focus on building reusable networks, learning from trials and consortiums that are paving the way.
- Recognize that there is shared accountability across organizations to make the required changes to achieve a learning health system.
Support sponsors, investigators, and operational technology providers to share learnings across the clinical trial ecosystem.

**Sponsors** should:

- Talk with senior level executives at health care institutions and determine what better integration of research into practice could look like.
- Explore alternate reimbursement approaches other than “per subject” to foster development of a financial infrastructure at the healthcare provider level.

**METHODS**

Experts and key stakeholders from across the clinical trials ecosystem developed these recommendations following CTTI’s five-step methodology* design to ensure the recommendations are actionable, evidence-based, and consensus driven.

These recommendations were informed by qualitative, in-depth interviews with designers and implementers of embedded interventional clinical trials in clinical practice, as well as input from a multi-stakeholder project team and a multi-stakeholder Expert Meeting.

*https://doi.org/10.1177/174077451875505

**REFERENCES**


Stakeholder Input to Optimize the Design of an Embedded Trial

The following is a list of stakeholders that trial designers should consider engaging to optimize the design of an embedded trial.

- **Health care providers:** To provide insight on health care priorities, help formulate and revise the research question, and weigh-in on clinically relevant endpoints that could be captured in routine care. Clinicians, and allied health care professionals such as nursing and pharmacy staff, are also well versed in logistics of implementation, including burden and time commitment, integration of the intervention into clinic workflow, reimbursement for clinician time and research program support, training, and likely enrollment numbers at a clinic.

- **Patients and patient groups:** To appreciate where and how they are getting their care and to identify meaningful endpoints. Patients should also advise about consent forms and the consenting process and be advocates for equity, inclusion, access, and diversity during protocol design.

- **Trial design and statistics experts:** For design options, including data management and statistical methods when using data from real world sources.

- **Funding agencies:** For early input in the embedded trial design if seeking grant support.

- **Regulators and Health Technology Assessment bodies:** For input on whether the trial design and data, including use of real world data, can adequately address the research question.

- **IT and informatics:** To assist with trial design and setup, especially related to programming for trial-specific needs for accessing, sorting, and extracting data from the EHR or other real world sources.

  For example, IT providers can assist sponsors with assessing EHR data in relation to clinical practice patterns and their variability (e.g. frequency of visits, diagnostic testing or monitoring, how often medications are switched or renewed).

For additional recommendations on when and how to engage stakeholders in clinical trials, see CTTI projects on Engaging Stakeholders, Patient Engagement, and Quality by Design.