WHITE PAPER

Planning Real-World Studies to Support Cell and Gene Therapy Evidence Generation Needs

Demonstrating long-term outcomes that enable access to as many patients as possible

UBC

The Rising Wave of Cell and Gene Therapies

Cellular and gene therapies (CGTs) offer a personalized approach to medicine for patients who have previously had few or no options, including those with rare diseases, genetic disorders and cancer. The number of CGTs entering clinical trials and obtaining regulatory approvals is increasing every year. According to the Alliance for Regenerative Medicine, there are currently more than 2,000 CGT clinical trials underway globally, approximately 200 of which are in Phase 3 development[1]. As of January 2023, the U.S. Food and Drug Administration (FDA) has approved 27 CGT products and the EMA has approved 24 CGTs[2], referred to as Advanced Therapy Medicinal Products (ATMPs).

Leveraging Real-Word Data and Evidence to Overcome CGT Study Complexities

CGT STUDY CHALLENGES

Unlike other medical products, CGTs often involve new or costly manufacturing technologies and have long-term or life-long effects. This can translate into prolonged research and development cycles followed by drug access challenges. In brief, patients can expect a complex path to an ultimately costly treatment. This means that sponsors need to demonstrate long-term outcomes that enable access to as many patients as possible. Effectiveness and safety outcomes must be demonstrated to satisfy patients, providers, regulators, and payers/Health Technology Assessment (HTA) bodies.

Sponsors developing CGTs face multiple challenges throughout the product lifecycle that can potentially be addressed with real-world data (RWD) or real-world evidence (RWE):

- **Patient recruitment:** CGTs generally treat small patient populations that are geographically dispersed. Often, there are only small numbers of specialized centers that can treat these patients, with no guarantee that they are close to patients. As such, patients may find travel to sites prohibitively difficult, depending on the disease state.
- **Direct comparators:** CGTs often treat patient populations for which there are no therapeutic alternatives or known natural history information, making it challenging to establish appropriate outcomes or benchmarks. It may be unethical to utilize placebo controls in these populations, which means alternatives to Randomized Controlled Trials (RCTs) may be needed.
- **Long-term follow-up (LTFU) commitments::** The FDA and EMA require post-marketing surveillance activities to establish real-world effectiveness and safety for CGTs.
- **Access:** With uncertainty around the long-term benefit of CGTs and the high cost of these therapies, payers and HTA bodies must balance evidence needs with allowing patients to access much needed CGTs.

U.S. FDA Definitions:

Gene Therapy[3]: technique that modifies a person's genes to treat or cure a disease. Gene therapies can work by several mechanisms:

- Replacing a disease-causing gene with a healthy copy of the gene
- Inactivating a disease-causing gene that is not functioning properly
- Introducing a new of modified gene into the body to help treat a disease

Gene therapy product types include plasmid DNA, viral vectors, bacterial vectors, human gene editing technology, and patient-derived cellular gene therapy products.

Cellular Therapy[4]: Cellular therapy products include cellular immunotherapies, cancer vaccines, and other types of both autologous and allogeneic cells for certain therapeutic indications, including hematopoietic stem cells and adult and embryonic stem cells. Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

For a full list of current FDA-approved CGTs, see www.fda.gov[5].

CGT Study Solutions

This white paper will focus on how thoughtful incorporation of real-world data (RWD) and real-world evidence (RWE) into evidence generation planning activities can address each of these challenges.

PATIENT RECRUITMENT

RWD sources, including but not limited to electronic health records (EHRs), medical claims, and disease registries, can be used to identify patients matching study criteria. Patients can also be identified geographically for targeted recruitment. Use of RWD-driven digital outreach to these patient populations can then be used to focus recruitment efforts. In combination with other patient-centric strategies that UBC has previously published[8], such as patient advocacy group engagement, RWD can serve as a powerful tool in optimizing patient recruitment strategies.

DIRECT COMPARATORS

RWD (e.g., from patient registries, medical charts, or clinical trial data) is a primary data source for constructing historical control datasets to supplement or replace control arms for clinical studies. Each data source has limitations that should be considered. For example, registries frequently have missing data, even when standardized. This is often because "usual care" can differ across sites. While medical charts tend to be more comprehensive, patient selection bias may be introduced, as patients from clinical trials tend to show better outcomes than those in routine clinical practice. To minimize selection bias or differences among groups when using historical clinical trial data, it is important to consider demographics, study design and quality, inclusion and exclusion criteria, and other factors.

Using prospective natural history studies as a comparator arm is another approach to obtaining comparative data. These studies are often conducted ahead of or concurrent with early phase development to establish the current course of the disease. If carefully and thoughtfully designed, the data generated in a natural history study can be used as an external control group for regulatory submissions. These studies differ from registries in that they can be designed to collect data that is comprehensive and specific to the disease being investigated.

When using RWD sources to construct comparator arms, sponsors should identify the most appropriate data source(s) and establish a data analysis plan that can adequately address stakeholder concerns. UBC has previously published considerations for addressing the statistical analysis plan for RWE studies, from defining the research question and planning the study design to preparing and cleaning the data and addressing confounding and bias, and finally, interpreting and reporting the statistically analyses results clearly[9].

LONG-TERM EFFECTIVENESS

RWE is critical in demonstrating long-term outcomes beyond clinical trials. RWE can play a role in regulatory approval, as well as in the post-approval environment to meet the needs of regulators, HTA bodies, and payers. However, each stakeholder will have their own data requirements, data standards, and policies for accepting RWE.

REGISTRIES & INTEGRATED REGISTRIES

Both the EMA and FDA have provided guidance for using data registries in regulatory decision-making and for the implementation of post-marketing requirements[10-11]. For approved products with LTFU commitments, registries can be designed to collect data on standard of care practice. These can be newly initiated prospective registries or integrated registries. In many rare disease and gene therapy indications, registries are in place, sponsored by advocacy groups or single institutions or

European Medicines Agency (EMA) Definitions[6]:

Advanced Therapy Medicinal Products (ATMP): medicines for human use that are based on genes, tissues or cells. ATMPs can be classified as follows:

- **Gene therapy medicinal product (GTMP):** contain genes that lead to a therapeutic, prophylactic, or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer, or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.
- **Somatic cell therapy medicinal product (SCTMP):** contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose, or prevent diseases.
- **Tissue-engineered therapies (TET):** contain cells or tissues that have been modified so they can be used to repair, regenerate, or replace human tissue.
- **Combined ATMPs:** ATMPs that contain one or more medical devices as an integral part of the medicine.

For a full list of current EMA-approved ATMPs, see www.ema.europa.eu[7].

consortia. However, these may be geographically limited and lack a uniform data collection format. An integrated registry can combine and harmonize the data from various independent registries. This combined data asset can also be enriched with data from other RWE sources or prospective data generation. Effectively integrating registries requires a combination of data science and technical expertise. It is vital to understand essential technologies that enable data integration and harmonization, including data linkage and tokenization, and ingestion and standardization of data from disparate sources into a common data model. UBC previously presented the case study in Figure 1 to illustrate how integrated registries that are linked to RWD are beneficial[9].

DECENTRALIZED TRIALS (DCT)

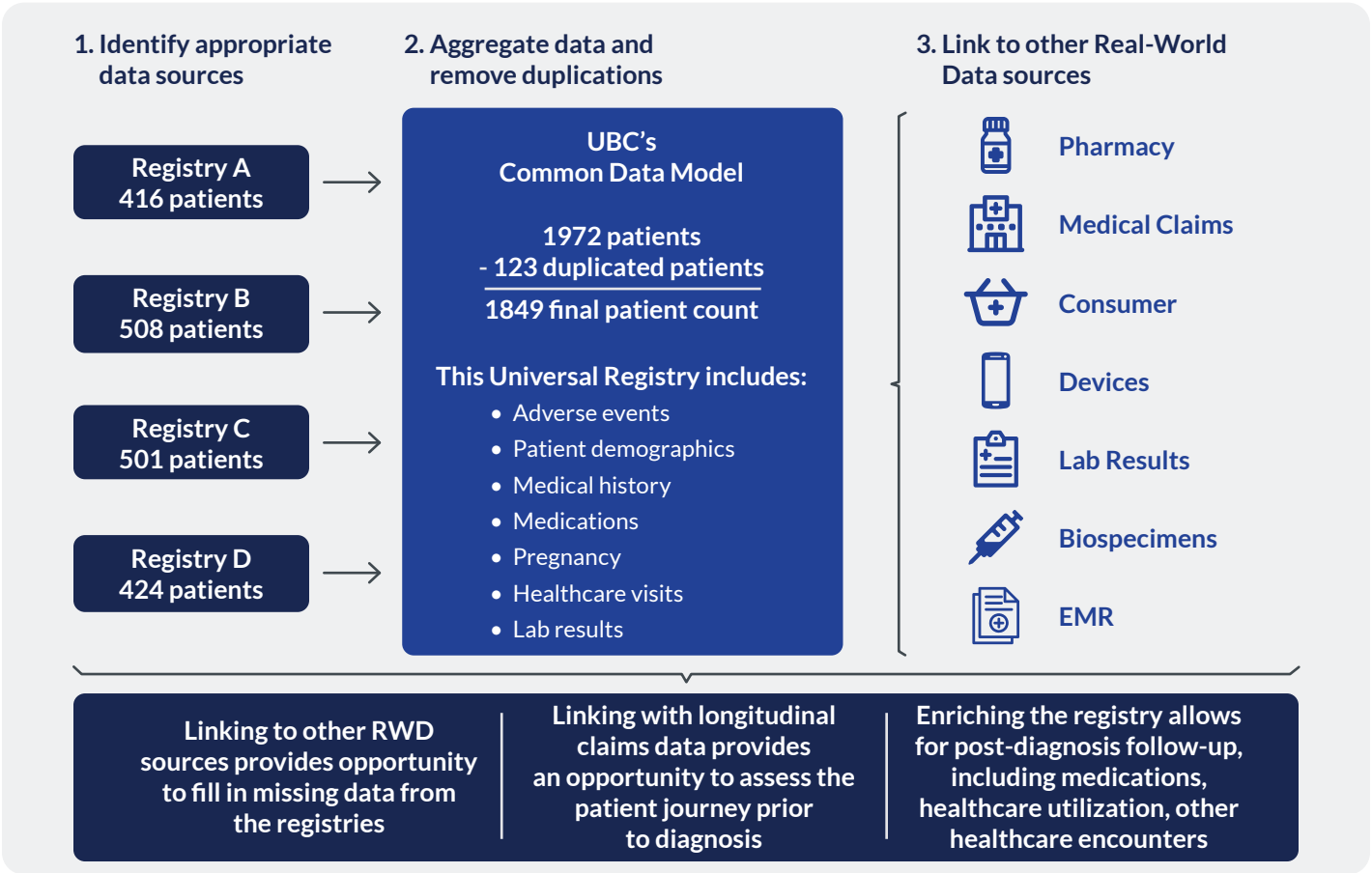
LTFU commitments can span from five to fifteen or more years. Over this time, patients' lives will change, and technology will transform. It is paramount to design a flexible study that can adapt to these changes. DCT approaches that bring the study to the patient allow for more efficient and robust data capture. They can expand patient populations, maximizing the data capture on patients treated in the commercial CGT setting. Trials with DCT elements can accommodate a population that moves out of pediatric care, goes to college, and becomes more mobile. More detail on decentralized approaches has been published in UBC's Decentralized Research Playbook[12] to help sponsors plan, prioritize, and educate internal stakeholders on the planning and execution of studies incorporating decentralized elements. UBC previously presented the study in Figure 2 illustrates the benefits of DCT approaches[8].

ACCESS

Difficulties associated with patient recruitment for CGT studies and the technical complexity associated with these therapies often result in smaller clinical trial populations that may not be representative of real-world populations. At product launch, the lack of strong evidence for effectiveness results in affordability issues for payers who are relying on limited clinical trial data to inform coverage decisions of what are traditionally high-cost and potentially one-time use therapeutics. This also hinders routine

Figure 1: Case Study: Integrated Registry Enriched with RWD

This case involved integration of four separate registries for a rare disease. Deduplication of patients is a necessary step when integrating registries. Creation of a common data model includes considerations of coding structure, level of completeness of the data and data sources[9].

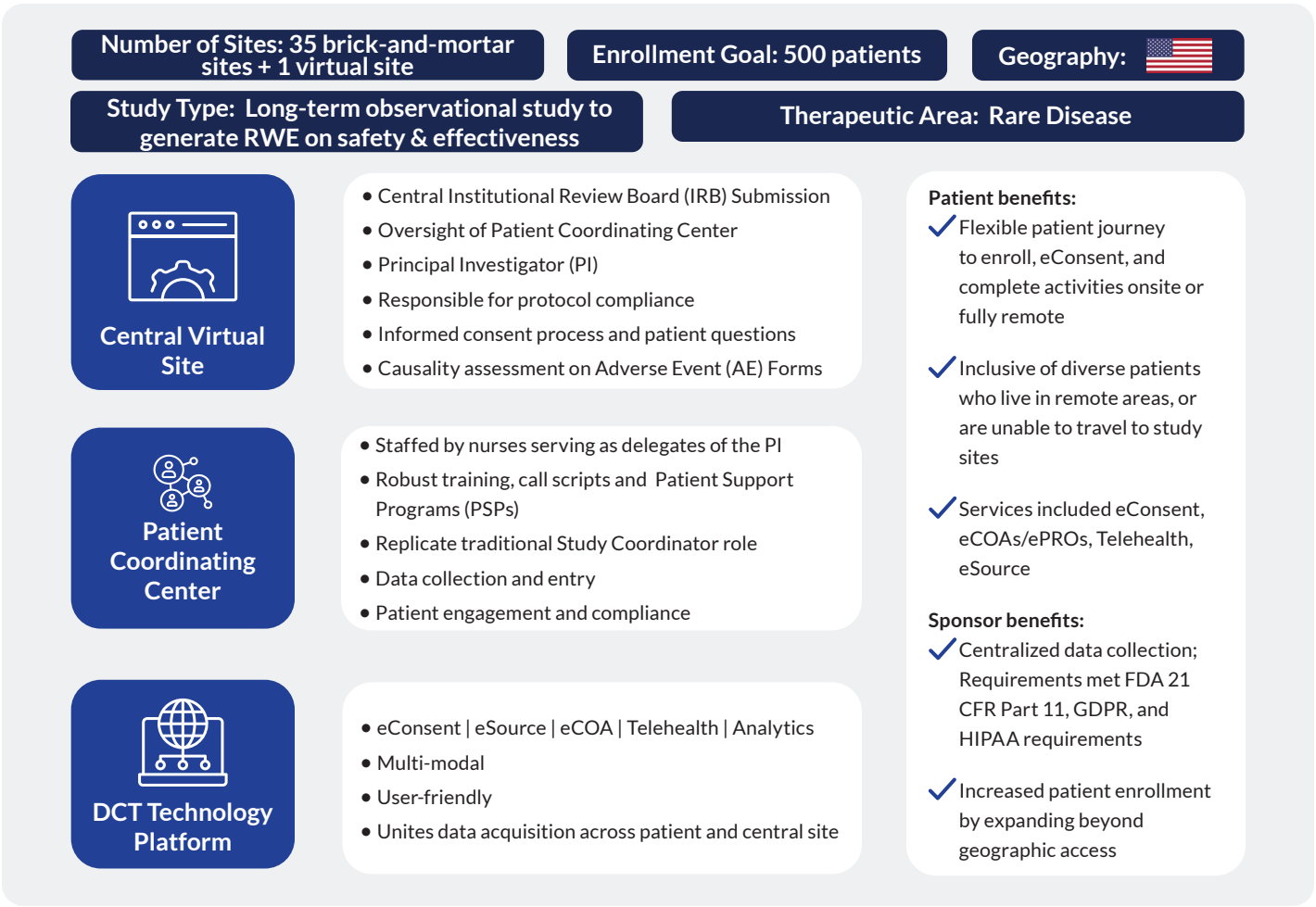


clinical use of cell and gene therapies. Strategic incorporation of RWD from post-approval clinical use (e.g., from registries, EHRs and other sources) provides additional data to support therapeutic effectiveness. Registries, in particular, play an important role in monitoring the safety and effectiveness of therapeutics and strengthening the evidence base, allowing for long-term follow up of patients in the real world. Resulting RWE can help to reduce payer uncertainty around clinical data leading up to launch. Coverage strategies including RWE may include conditional reimbursement options, pay-for-performance or outcomes-based coverage models, and other innovative approaches that provide access to these much-needed therapeutics.

Demonstrating Value with an Integrated RWE Generation Strategy

As the CGT landscape continues to evolve, sponsors are adopting modern approaches in RWE study design and data analysis that can support product value demonstration for regulators, but also for other external stakeholders, including patients, payers, and providers. When planned *a priori*, RWE studies can be designed to satisfy the needs of internal cross-functional partners as well as external stakeholders. Planning an integrated (clinical and real-world) evidence generation strategy during pre-marketing phases of development is a first step toward demonstrating product value in the real world.

Figure 2. Case Study: Decentralized Research Tactics to Augment Brick-and-Mortar Studies



About UBC

United BioSource LLC (UBC) is the leading provider of evidence development solutions with an expertise in uniting evidence and access. UBC helps biopharma mitigate risk, address product hurdles, and demonstrate safety, efficacy, and value under real-world conditions. Bringing over 30 years of experience, UBC is uniquely positioned to develop end-to-end integrated evidence generation strategies, identify fit-for-purpose data sources, operationalize planned studies and ensure regulatory-grade, publishable outputs.

To learn more about how UBC can help you develop an integrated, real-world evidence strategy for your CGT, reach out to us at contact@ubc.com.

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