Chapter 16

Data Unit, Translational Research, and Registries

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Research is the core competency and the third most crucial pillar of any major cancer center, followed by patient care and teaching. Research and development is a dynamic process with a myriad of dimensions, applications, and deliverables as the backbone of evidence-based medicine. If planned and executed correctly, it can yield huge dividends as per the center's mission, vision, and lines of effort. Establishing a center of excellence to deliver world-class medicine is the patients' right and the state's obligation. Collaborative research with locoregional and international partners to offer the most advanced cancer care with dignity, respect, and the best possible QOL is noble. Challenging the existing standards of care and continuously improving cancer care is the silver lining of research. Cancer research has morphed into a tremendously relevant role for more comprehensive and long-term approaches. Shifting the paradigm, achieving new pinnacles by administering most innovative and novel therapies, devices, interventions, and techniques remain the primary objective of research for improving survival outcomes. Clinical research has witnessed unprecedented growth in recent years and has emerged as an area of high priority. Health improvement and optimization is directly linked to global security. The robust leadership, culture of research, continuous quality improvement, and research infrastructure are the cornerstones of the most efficient cancer care for measurable and quantifiable outcomes [1].

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Research Data Unit

The research unit serves as an institutional hub for initiation and registration of clinical trials by the clinicians/investigators, monitoring accrual to each protocol, budget negotiation, clinical trial agreements for research trials, and developing SOPs to facilitate centralized management of clinical studies. The research unit aims at providing the best possible quality care and a wide array of investigational therapeutic options to patients with highly advanced cancers, which would not be available otherwise. A well-structured research unit can be of immense help in streamlining and increasing efficiency for quantifiable and measurable outcomes. It is well-positioned for patient safety, higher recruitment and retention rates, quality data, and reduced study timelines and costs. The most commonly used staffing models in the research unit are team-based model (individual PIs head separate research team) and a more traditional centralized model (research supervisors assign research and support staff from pooled department resources to individual PI for each project). Research unit manages the design, conduct, approval, and analysis of research by providing comprehensive data management support to researchers as per the IPPs for efficient, quality, and statistically sound research outcomes as follows:

- *Staffing:* Qualified and trained research staff with adequate process knowledge are pivotal for data management, multidisciplinary coordination, biological specimen processing/handling, and managing regulatory issues. Research staff is responsible for designing Case Report Forms (CRFs), documentation, database designing, data entry, data validation, discrepancy management, adverse events reporting, and data extraction. Research staff provides the support and conducive environment for the investigators and clinicians to conduct for locoregional and international clinical trials/registries/databases (from proposal inception to publication) as per the local and international standards (ICH-GCP, CIOMS, NIH OHRP, Declaration of Helsinki).
- *Data management:* Research unit supports the researchers during the entire life cycle of a clinical trial by determining patients' eligibility, screening, workup, informed consent process, randomization, follow-up, protocol-specific procedure as per the timelines, data entry, regulatory compliance, pharmacy coordination, quality assurance, risk communication/reporting, document submission, and management for enrolled patients of research protocols. Data accuracy, reliability, and consistency are the minimum essential requirements for quality research programs. A wide variety of data management e-tools are being used to efficiently capture, store, and process tremendous amounts of data from multiple sources in one central platform for high-quality output. The most used commercial software are RAVE, ORACLE CLINICAL, CLINTRIAL, MACRO, and eClinical Suite as per the Code of Federal Regulations (CFR), 21 CFR Part 11. Some of the open-source software are TrialDB, openCDMS, OpenClinica, and PhOSCo. SOPs and control measures of the research unit ensure the integrity, confidentiality, and authenticity of research data.

- *Regulatory compliance:* The roles and responsibilities of the research unit include the development and implementation of research protocols, administrative support, regulatory support, monitoring subject accrual, and providing support for institutional leadership. Supporting clinical/translational review committees, data and safety monitoring committee, and QA committees in addition to continuing education and training for research staff are done by the research unit. Regulatory compliance is pivotal for generating high-quality data for an accurate trial outcome.
- *Investigational drug management/pharmacovigilance:* Research unit provides effective stakeholder coordination for study-specific drug shipment, dispensing, and administration as per protocol. Adverse drug reaction reporting, pharmacovigilance, risk management, and patient safety are critical elements of clinical research and are addressed, monitored, coordinated by the research unit through effective communication and robust teamwork. Patient safety monitoring during research studies is a critical component throughout the conduct of the study and requires effective and timely communication among all the stakeholders.
- *Quality assurance:* It is the fundamental process for generating high-quality, accurate, reliable, complete, and suitable data for statistical analysis as per protocol parameters and requirements. QA is the best way to determine protocol deviations and noncompliance. Quality data have minimal unknown or missing variables and acceptable level of protocol deviations in accordance with regulatory requirements specified for data quality. Periodic QA site visits and audits are conducted by the sponsors for protocol compliance. Institutions also have built-in internal and external audit programs for continuous quality improvement.

Translational Research (TR)

TR encompasses multidisciplinary and multidirectional coordination of laboratory and clinical research to enhance disease control and improve survival. The purpose of this bench to bedside approach is to facilitate the application of newly acquired knowledge to the patient, effectively and expeditiously, to maximize the benefit, minimum adverse events, and optimize the treatment outcomes. Translational research is the application of laboratory research innovations through preclinical studies to the patients in the clinic through clinical trials with agility to improve health outcomes. Translational research can be divided into three domains: From bench to bedside; from bench to public health; and industrialization of medical research processes. TR requires very close collaboration between the clinicians and the scientists through effective teamwork and communication. Continuous funding helps maintain the infrastructure and the minimum essential manning for the research facilities. Quality management is a pivotal part of the translational research.

Paradigmatically contextualized within the emerging purview of oncology research, translational research has become a vital tenet of accelerating research into complex cancer treatments that conflate a balance between costs of

administration, primary effectiveness, and adverse implications on patient well-being. Axiomatic translational research entails the creation of an unimpeded continuum of clinical dynamics which encapsulate both clinical and basic research. The purview of collaboration rectifies the capacity for clinicians to accelerate the transition from bench to bedside. The insidious implications of ineffective collaboration are amplified amongst singular basic research institutions whose activity is contingent on the clinical care conducted by surrounding institutions, ensuring a streamlined approach to collecting adequate data samples measuring drug efficacy. Further establishment of lines of communication between all constituent actors involved across the research continuum facilitates the rigorous testing required to ensure the viability of potential cancer medications, cultivating long-term prospects for the most effective remedial practices. Stagnated collaboration has the potential to instigate debilitating parameters for further innovative oncological research not conducive to the rapid conditions required to venture into all ostensible treatments. Collaboration, however, entails robust leadership with an emphasis on the creation of standardized quality guidelines across all disciplines embedded within the mechanism of translational research. Standardized guidelines, pertaining to clinical follow-ups and procedural methods, would ensure mitigation of potential discontinuities arising across the interdisciplinary, diverse translational research team. Furthermore, standardized guidelines for translational research would essentially streamline all subsequent trials, preventing the need to pursue trial and error strategies for clinical implementation of research practices.

The equitable dissemination of research-related expertise, resources, and technical knowledge would ameliorate more efficient research processes, thus potentially facilitating an increased capacity for diverse research activity simultaneously. Concurrent mechanisms, notably the demand for a streamlined accessibility of foundational resources to facilitate the unimpeded transition from bench to bedside, is elemental in reconciling the gap along the continuum of research and preventing the stagnation of novel research. Funding allocated towards the fields of data transfer for the dissemination of information characterizes the remainder of clinical testing subsequent to embracing its transition from the bedside, shifting crucial information from clinical results to the preclinical investigator who seeks to discern any potential adverse outcomes from the experimental treatment.

Registry

One of the most efficient instruments of data management is disease-specific registries to generate high-quality, reliable, and statistically sound data. These registries, frequently referred to as outcomes registries, are “organized systems” that use observational study methods to collect uniform data. Specified outcomes are evaluated by the disease-specific registries for predetermined clinical, scientific, and administrative end state. Currently, myriads of local, national, regional, and international registries exist to collect information about cancer outcomes. These registries

have played a pivotal role in determining trends, patterns, treatment practices, toxicities, patterns of failures, and survival outcomes.

Wide array of registries exist, globally, each with a well-defined and specific aims and objectives. These registries are managed by academic institutions, cooperative groups, professional organizations, third parties, public and private authorities, or researchers. Registries vary in the type, depth, timeline, and outcome variables. Overtime registries are evolving to complement and collaborate with each other to provide even larger pool of data to expand future joint research activities. A critical development in the last few years has been the recommendations by the World Health Organization (WHO) that data capturing and outcome analysis needs to be essential element of treatment and mandatory instead of an option for transplant centers. This chapter will focus on establishing an effective prospective institutional database with a silver lining in ensuring data quality and functions of HSCT registries by highlighting the processes involved and tools and standards adopted along with the roles and responsibilities of the team members. It will further highlight the challenges faced in reporting to international outcome registries, including CIBMTR, EBMT, and others.

Registry Fundamentals Observational data is highly valuable research tool in assessing utilization and patterns of medical care as well as facilitating outcomes analysis to fill evidence gaps regarding safety and effectiveness. Patient registries, typically referred to as outcomes registries, are the “organized systems” that utilize observational study methods to collect uniform data to assess predetermined outcomes for a particular exposure or disease. Highly valuable registry output serves as the rationale for future scientific and clinical trials or policy purposes [2]. Registries can be classified according to how their populations are defined and their objectives. Populations may be defined according to disease or conditions, exposures such disease managements, interventions, or side effects, or other variables like socioeconomic status. Registries are most used to capture demographics, exposures, or natural history of disease, treatment efficacy, safety, complications, adverse events, quality of life, and changing patterns of disease in an organized manner.

Registries facilitate research by addressing questions difficult to answer by clinical trials [3] or complementing clinical trial findings [4]. If data collection is sufficiently comprehensive, outcome analysis from registries could be broadly generalizable. Registries can be pivotal in continuous quality improvement, maximizing patient care, and reducing complications by reporting loops and data feedback.

Registries based upon international ethical and quality standards are considered of high scientific value for outcome analysis. Easy accessibility, credibility, accuracy, integrity, and confidentiality are the essential ingredients of a quality registry. Registries can promote research in the region, identify locoregional trends and practices, standards, and interventions, and may also be helpful in benchmarking disease outcomes. Comparison with European Group for Blood and Marrow Transplantation (EBMT) registry has shown that national registries can be used to benchmark outcome using the EBMT registry as reference [5]. The Center for International Blood

and Marrow Transplantation (CIBMTR) assesses yearly survival after allogeneic HSCTs in each of the US transplant centers for participating centers and the public [6, 7]. Globalization of HSCT donor and patient registration is a realistic goal and could lead to donor safety, better treatments, and outcomes [8, 9]. Registry data have provided important insights into international differences in indications for HSCT, and access to HSCT [10]. Data from outcome registries is helpful for comparative analysis to further refine therapeutic intervention and improve outcomes. Outcome registries face a myriad of challenges and are summarized as follows:

Research Personnel Adequately qualified and properly trained research professionals with sound medical background and experience with multidisciplinary approach are essential. Critical experts in the operation of the registry include clinical/scientific, project management, biostatistics and epidemiology, data managers, database administrators, regulatory compliance, and expertise in quality assurance. Staff familiarization with basic principles of cancer epidemiology, terminology, therapeutic interventions, and outcomes can substantially increase the value of registry. Cohesive teamwork is the key for optimizing the value of the registry throughout the registry life cycle by data capturing, analysis, dissemination, reporting, and publications.

Regulations – Managing Ethical, Privacy, and Legal Considerations Maintaining privacy and confidentiality, protection of human subjects and legal issues in data management (ownership, collection, and data exchange) are the major tenets of registry. Robust security mechanisms are crucial to safeguards the rights of registry participants, especially for the registry involving international collaboration. The bylaws, data transfer agreements, accreditation for standardization are pivotal in streamlining regulatory trepidations. However, wide-ranging variations in IRB regulations and cultural sensitivities can be challenging, especially for multinational registries. However, because outcomes registries are observational, they are often considered “low risk” with regard to the potential for harm to human subjects. The registry must address consent for the use of data for research obtained from research subjects by outcomes registries; however, registry functions for public health or government program purposes may not require specific consent for research [11].

Data Management Scope and quality of data determines the usefulness of a registry. The scope of the data collected is framed by purpose and objectives and is influenced by myriad factors (geographic location, setting of data collection, cost). The size of the registry can vary depending upon the number of observations required to achieve the desired end states.

Registries have well-defined core dataset of essential data elements and patient outcomes as per the purpose and objectives. Core data sets and CRFs are reviewed and revised periodically to align with evolving diagnostic, therapeutic and prognostic markers. Accuracy, integrity, and data completeness are the most critical elements in the quality and value of a registry. Most data collection for HSCT outcomes registries is conducted using electronic applications. Sound quality information systems are needed for effective data collection to support the registry.

Cultural Sensitivities and Communication Issues Particularly, international registries are managed by continuous education and training in a unified manner to overcome tremendous cultural, social, and economic heterogeneity. Culturally sensitive tools (QOL form, etc.) can help enhance registry compliance.

Performance/Quality Management Registry (e.g., HSCT) can be a crucial component of a center's quality management/performance improvement programs. The accreditation bodies for HSCT in the US and Europe (FACT, ISCT, EBMT-JACIE, etc.) mandate that transplant centers collect and utilize standard core dataset defined by the field to analyze and understand their program quality [12]. Accreditation helps in implementing basic unified standards for good clinical practice among all participating centers for accuracy, integrity, and transparency of registry data. Outcomes registries can also provide a quality context or benchmark for HSCT centers when evaluating their program's performance. Quality management research can also be facilitated by outcome registries, which can lead to better survival outcomes by improving transplant practices. Registries facilitates uniformity in lab standards, toxicity criteria (Bearman) [13], GVHD definitions (National Institutes of Health [NIH] [14], and performance status (Karnofsky Performance Status [KPS], Eastern Cooperative Oncology Group [ECOG]/Zubrod, etc.). High-quality registry encompasses advanced methodology, operational excellence, enhanced validity, and discernible outcomes.

Data Utilization and Publications Observational research findings yield in significant clinical improvement and clinical trial planning [15]. Data sharing and collaborative research for optimizing patient outcomes is the key to a useful registry [16–17]. Many cancer centers report their data to comprehensive global registries (CIBMTR, EBMT, etc.). Interoperability, interfacing, and integration can maximize outcome and utility of these registries. Well-outlined and clear authorship guidelines are followed and unanimously approved by the participating centers based upon the number of patients, intellectual contributions, and center participation. Registry enhances the understanding of disease outcomes by addressing key questions like intervention results in specific patient groups, prognostic factors, new therapeutic regimens, comparison of therapies, inter-center practice, and outcome variability, capturing delayed adverse events and novel analytic approaches [18].

Registry can help in determining the efficacy of innovative and novel therapeutic strategies, assess outcomes, accrual patterns, generalizability, and patient selection practices. Registries can provide valuable data for well-designed retrospective observational studies to improve clinical practice [19–21] and plan future clinical trials [22].

Funding and Sustainability Registry operations to collect complete, high-quality data are resource-intensive and funding-dependent. Sponsors include government agencies, scientific grant organizations, research collaborators, pharmaceutical manufacturers, accreditation bodies, philanthropic organizations, and others. Funding could be for the overall operations of the registry or a specific research project. Some sponsors may have vested interest, and partially fund the registry, for capturing the utilization data of a particular product, device, or intervention.

Outcomes registries must remain vigilant for an innovation or collaborative opportunities to use or expand the registry to seize new funding opportunities.

Conclusion

There is a growing need to develop high-quality research infrastructure in newly developing cancer centers. Existing international models are a great resource for adopting best practices in establishing the research unit with advanced capabilities and procedures for data capturing, data quality monitoring, data analysis, strategic communication, and publications. Well-positioned, fully operational and optimally functional research unit should be able to provide highly valuable information and data that would not be available otherwise. The data quality standardization is vital to determine the scientific credibility and reliability of a research entity. A critical development in the last few years has been the recommendation of the World Health Organization (WHO) to make the data collection and analysis an integral part of the therapy rather than a choice for cancer programs.

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