Chapter 15

Data Management

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Data Management

Hematopoietic stem cell transplantation (HSCT) is a multidisciplinary and definitive treatment modality for myriads of life-threatening conditions. HSCT has witnessed tremendous development and evolution since its inception and has emerged as an area of high priority. Traditionally, HSCT has been used and continues to expand as a definitive treatment for multitudes of malignancies, inherited disorders, and bone marrow failures [1–3]. This growth has been witnessed not only in the developed countries but also in low- and middle-income countries (L&MIC). Cellular therapies have emerged as the most promising treatment modalities in HCT, and this trend is expected to continue.

HSCT databases are the backbone of any quality transplant program to achieve desired end states as per the institutional lines of efforts. These registries are organized systems to collate uniform data using observational study methodology to determine trends, patterns, and treatment outcomes in HSCT. The source documents for these outcome registries are mostly the patient's medical record. Transplant database encompassing complete, accurate, and reliable transplant data is geared toward capturing evolving trends, best practices, and resource allocation/utilization and streamlining multidimensional quality indicators for continuous quality improvement (CQI) and optimal outcomes. Data management is crucial for determining trends, developing quality observational studies, and answering the

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questions that can't be answered otherwise to improve HSCT knowledge globally. Observational registries provide state of current knowledge and gaps in evidence to form the basis for prevention/intervention programs, delivery, and effectiveness. They can help in designing the optimal schema for prospective and retrospective studies and for comparative analyses of diverse HSCT strategies for HSCT vs. non-HSCT therapies. Registries are particularly useful in situations where a comprehensive and flexible research design is needed or when the purpose is to discover how a product works in a wide variety of sub-groups, including ethnicity and socioeconomic status. A hybrid approach registry collects data retrospectively and prospectively. If data collection is sufficiently comprehensive, outcomes findings from patient registries can be widely generalizable. Rapidly evolving HSCT technology and widely varied outcomes among diverse patient populations need to be balanced with data management support.

Transplant databases are aimed at monitoring the natural history of the disease, demographics, therapeutic interventions, toxicity/safety, treatment effectiveness, quality assessment, and sustainability of this high-stake tertiary care service in a systematic approach. Short- and long-term complications of HSCT require long-term follow-up of patients. Databases and the consent formats need to be approved by the Institutional Review Boards (IRBs) as per the local rules and regulations and the Standard Operating Procedures (SOPs). Data managers (DMs) play a significant role in capturing contemporary knowledge about the indications, stem cell utilization, benchmarking data quality, and assessing outcomes for better resource planning/allocation/utilization [4]. Minimal essential data on each transplant recipient and donor can be captured using EBMT and CIBMTR minimum essential forms (MED-A), and Transplant Registry Unified Management Program (TRUMP) by the APBMT, the survey form of the EMBMT, and other organizations. The HSCT database is pivotal in conducting innovative observational registry studies, providing a platform for clinical trials, and enhancing transplant outcomes. Qualified, trained, and experienced personnel are essential to initiate and maintain such registries [5]. Data managers are required for quality data management and their continuing education and training, and interdisciplinary teamwork is critical for the optimum use and outcomes of the HSCT databases [6]. Precision, communication, collaboration, and close coordination are crucial for achieving the desired end states. High-quality transplant program data management encompasses advanced methodology, operational excellence, enhanced validity, and discernable outcomes (Table 15.1). Changing trends and patterns in personalized medicine have underscored the importance of data management to ensure that all cellular products are being processed as per protocol, safety standards, and guidelines to optimize disease outcomes. Data management is a dynamic process with myriads of dimensions, applications, and deliverables as the backbone of quality HSCT program, leading to evidence-based medicine. If designed and executed correctly, it can yield huge dividends to fill in the knowledge gaps and support the center's lines of effort (Table 15.2).

Data management is pivotal for a high-quality HSCT program to identify challenges, find solutions, and overcome potential barriers to maximize clinical and patient-reported outcome measurements (PROMs). Following guidelines and

Table 15.1
Fundamentals
of data
management

<i>Qualified personnel</i>
Trained and qualified personnel
Familiarity with staging, grading, toxicity criteria
Teamwork/effective communication/collaboration/ multidisciplinary approach
Cross-training of research coordinators/data managers
Workload, proportionality, and time management
<i>Regulations</i>
SOPS/IPPs/by-laws, data/material transfer agreements
Accreditation for standardization (JACIE/FACT/etc.)
Ethical committee/IRB regulations
Informed consent issues
Central Institution Review Board (CIRB)
Privacy and confidentiality
<i>Data processing</i>
Documentation: accuracy and integrity
Source documents: case report forms (CRFs)
Harmonized forms (uniform use of standardized data elements/ definitions)
Linking data sources for efficiency
Data quality/comparability/standardization
Data monitoring safety board/committee (DMSB)
Quality assurance and performance improvement (QA/PI)/audits
Electronic data capturing (EDC): long-term follow-up data
<i>Medical record</i>
Electronic (EMR)
Paper-based (charts)
Hybrid
Training and in-service
<i>Standardized data management software</i>
Uniformity, standardization
Globally acceptable/compatible
<i>Communication and cultural issues</i>
Language barriers
Cultural, social, and economical heterogeneity
Cultural sensitivities/QOL instruments
<i>Quality management</i>
Homogeneity and uniformity of the databases
Accreditation standards: JACIE/FACT
Variation in labs/toxicity criteria/performance status (PS)
Annual review of database: new variables, biomarkers, staging/ grading

(continued)

Table 15.1 (continued)

<i>Data utilization and publications</i>
Overlapping registries/databases
Integration/interfacing/interoperability
Access to data
Authorship guidelines
<i>Funding</i>
Sustainable funding sources for long-term follow-up
Quality data generates new funding sources

Courtesy of Hussain et al. [11]

Table 15.2
Dynamics of data
management
in research

<i>Benefits of effective data management</i>
Identifying population
Fulfilling gaps in knowledge
Monitoring transplant trends/outcomes
Resource allocation – priority setting
Advocating for improved health care
Serving as a distribution mechanism
Facilitating establishment of communication network
Synchronization
Ensuring streamlined global data
<i>Principles of data collection</i>
Accuracy
Reliability
Validity
Simplicity
Completeness
<i>Minimum requirements</i>
Data collection/source documentation
Attributable, legible, contemporaneous, original, and accurate
Personnel
Regulations
Communication
Quality assurance
Funding
Data utilization/sharing/publications
<i>Quality assurance</i>
Standardization/accreditation
Uniform QM standards
Audits/site visits (internal and external)
Implications/outcomes of data quality

Courtesy of Hussain et al. [11]

recommendations from the CIBMTR, EBMT, WMDA, and Worldwide Network of Blood and Marrow Transplantation could be an effective way of streamlining data management issues for the HCT programs. However, following the data standards set forth by the HSCT accreditation bodies in the USA (Foundation for Accreditation of Cellular Therapy [FACT]) [7] and in Europe (Joint Accreditation Committee of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation [JACIE]) [8] is the ideal way to promote improvement in data quality of the HSCT program from harvesting to grafting. Regional transplant registries can promote HSCT in a specific region and identify locoregional trends and practices, standards and interventions, and benchmarking outcomes. National registries can be used to benchmark transplant outcomes using the large multinational outcomes registry (EBMT, CIBMTR, EMBMT, APBMT, etc). As a reference, CIBMTR carries out an annual assessment of one-year survival post-allogeneic HSCTs in each transplant center in the USA and provides it to participating centers and the public. The globalization of patient and donor registration for HSCT is a realistic goal and can contribute to the improvement of patient care, outcomes, and donor safety. Registry data have provided valuable insights into international differences in indications for HSCT and access to HSCT. Accuracy, reliability, and validity in data management are pivotal for quality improvement, the efficiency of care, and donor/recipient outcomes. Therapeutic outcomes of HSCT are optimized by utilizing myriads of clinical indicators encompassing transparency, close coordination, teamwork, and effective communication in a multidisciplinary approach (Table 15.3). Studies have shown a significant improvement in the donor and recipient care in the accredited centers by adhering to international

Table 15.3 Strengths of HSCT databases

Excellent source of demographic and activity data – dynamic measure of patterns of care
Useful for planning intervention trials – hypothesis generation and calculating effect size and potential recruitment
“Real-world” therapeutic effectiveness and safety data (as opposed to efficacy) – compare disease management by program, region, country
Heterogeneity of standard practice across participating sites facilitates research into “best practices”
Heterogeneity among study subjects
Detection of rare consequences is satisfied by large numbers of patients followed for long periods of time – a unique advantage
Low risk to participating subjects (observational rather than interventional) can promote broad participation
Flexibility: serves as a platform for extending observation or intervention to particular groups of subjects; sub-studies
Relatively low cost to develop and maintain on a per-patient basis
Useful as a comparative arm in comparative effectiveness research
Provide meaningful data for decision-making where a clinical trial is not feasible or practical
Approximation of treatment impacts is more realistic

Courtesy of Hussain et al. [11]

standards for optimal clinical, laboratory, and auxiliary practices in HSCT [9]. The databases' value is enhanced by following the universally acceptable ethical and quality standards for the design, collection, analysis, reporting, monitoring, and auditing of the data. Scientific rigor and transparency of the registry can be strengthened by following good registry practices. Easy access of registry data to the investigators and ensuring safeguards for credible, accurate, and reliable data are cardinal elements of a quality registry. Registries must provide assurance for the privacy, confidentiality, and integrity of data.

Quality management is crucial in the operational domain of a high-quality HSCT program for optimizing patient outcomes as per the existing SOPs and playbooks for efficient, quality, and sound therapeutic yields. The minimum essential elements of data management are as follows:

SOPs/IPPS/Playbook SOPs and control measures for HSCT data management ensure the integrity, confidentiality, and authenticity of transplant data. Documentation is crucial in setting up and maintaining a quality HSCT program as per the written SOPs or Internal policy and procedures (IPPs) to ensure that each team member is aware of its roles and responsibilities at the operational, strategic, and tactical levels. The playbook is pivotal for the continuity of quality data management by underscoring techniques, tactics, and procedure of data collection, quality assurance and outcomes to optimize operations planning and execution. It highlights the importance of what, when, where, who, why, and how to optimize the process flow in a multidisciplinary approach. The playbook provides a standardized and centralized guidance to conduct HSCT data management, record data into the appropriate data management system repository, and utilize the existing outputs to analyze, plan, and forecast future requirements and best practices. It also provides instructions for accessing the data management systems and generating reports and specific instructions for data capture support.

Trained/Qualified Personnel Qualified and trained personnel with adequate HSCT experience and process knowledge are pivotal to design, conduct, and manage the registries (processing, multidisciplinary coordination, and managing regulatory issues). Collaborative efforts of DMs can help facilitate registry activities from data acquisition to data processing and publications. The data management staff are responsible for the smooth flow of pre-transplant, transplant, and post-transplant care, documentation, validation, discrepancy management, adverse events reporting, and safety as per the local and international standards.

Data Processing The scope and quality of the data collected determine the value of an outcome registry. It's critical throughout the entire life cycle of HSCT by assessing donor/recipient eligibility, screening, workup, informed consent process, HLA matching, follow-up, protocol-specific procedure, data entry, regulatory compliance, pharmacy coordination, quality assurance, risk communication, document submission, and data management of transplant patients per treatment protocols. The purpose and objectives outline the scope of the outcome registry and are

affected by a myriad of factors. Size of the registry, complexity of the data elements and outcomes collected, number of observations, and duration are essential considerations to achieve registry objectives. A core dataset of crucial variables and patient outcomes are defined by the registry to accomplish its objectives. An internationally accepted core dataset has been developed by the major outcome registries (CIBMTR, EBMT) and is recognized internationally as a model for HSCT registries endorsed by the WBMT. Case report forms (CRFs) need to be revised periodically to ensure capturing of most current data (novel biomarkers, interventions, etc.). The reliability, accuracy, and validity of data are critical elements of a quality outcome database. Data comparability is crucial for interpretation and depends on the standardization of methodology and the diagnostic criteria utilized. Robust quality control can be achieved by regular internal and external audits, monitoring, and evaluation. Good quality, user friendly, cost-effective, reliable, validated, and compatible health information systems are essential for maintaining good quality outcome databases and registries [10]. Next-generation and web-based data entry applications, with efficient data validation tools, are required to streamline observational databases. Enhanced electronic data capturing efforts with built-in auditing and quality assurance tools can be very helpful in performance improvement, research, and publications.

Cultural Sensitivities/Communication There is significant cultural, social, and economic heterogeneity globally. Such cultural sensitivities and language barriers among diverse countries in a regional/international database/trial need to be addressed. Cultural sensitivities must be considered when collecting patient-reported information, like quality of life (QOL) data. Sometimes, certain QOL tools cannot be used for sociocultural reasons. Therefore, QOL forms should be culturally sensitive and validated.

Regulatory Compliance This is pivotal for yielding high-quality outcomes of transplant data and is monitored by internal and external regulatory authorities (IRB, Sponsor, FDA, etc.). Safeguarding patient safety, privacy, and confidentiality, with dignity and respect, while on research protocol is paramount. Developing and implementing SOPs/PPs, administrative and regulatory support, surveillance, and monitoring are critical quality indicators of the participant's privacy and confidentiality protection during collection, storage, and utilization of data. Supporting internal and external quality assurance site visits/audits, clinical review committees, Data and Safety Monitoring Boards (DSMB), morbidity and mortality (M & M) meetings, and QA committees are required elements of a quality data management program. Outcome registries and databases are often considered "low risk" in terms of the potential of harm to human subjects for being observational. Privacy concerns with regard to identifiable patient information can be addressed by registries by collection of de-identified data and collection of identifiable data for "internal use" with linked identifiers. A significant proportion of the annual HSCT performed globally use allogeneic donors acquired through a donor registry or a cord blood bank. Since most of the donor registries and cord blood banks are required to report

outcomes of products used for transplants, patient outcomes can be linked with the donor products with justification for identifiable information gathering. WHO has recommended that data collection and data analysis should be considered a mandatory part of transplantation programs following full ethical, legal, and privacy guidelines.

Pharmacovigilance Adverse drug reaction reporting, risk management, and patient safety are paramount for a transplant program and are managed by continuous surveillance, effective communication, and robust teamwork. During transplant, patient safety monitoring is a critical component throughout the transplant by precise coordination and communication among all the stakeholders.

Intellectual Property Rights, Data Utilization, and Publications Integration, interoperability, full access to each center's own data, and clearly defined authorship guidelines (based upon the number of transplants, contribution, and the center participation, etc.) are the pivotal success elements. Transplant data can be used to plan prospective HSCT trials in areas not well studied (role of geographical variations, genetic pre-disposition, genotypic and phenotypic variations, and biology of disease) by utilizing preliminary registry data. It can also be utilized to estimate outcomes and accrual patterns, sample size calculations, and implementation plans. Information about the most commonly used supportive care measures can be used to adapt protocols to standard practices and, thus, increase their acceptability in the transplant community. Comparison of clinical trial outcomes with observational outcomes can give an insight about generalizability and patient selection practices. The source of stem cells is highly influenced by chance for each patient, and in many occasions, it will not be possible to apply prospective randomization to answer some of the important clinical questions.

Funding and sustainability Collection of complete, accurate, and high-quality data is resource-intensive and spans over a long period. To be sustainable over the protracted time frame, long-term financial support is required. Consideration of the intended uses of the transplant database and those sponsors who can derive value from registry information (government/non-governmental agencies, scientific organizations, research collaborators, biopharmaceuticals, accreditation bodies, philanthropic organizations, etc.) could provide additional funding support. In the context of the contract for the US Stem Cell Therapeutic Outcomes Database, the CIBMTR derives substantial funding from the Department of Health and Human Services to support its outcomes registry operations. As an outcomes registry develops robust information, it can be a rich source of data for research, and grant funding to support research represents an excellent opportunity. Biopharmaceuticals or device manufacturers may have an interest in registry data to better understand utilization of their products, and short-term projects or long-term reporting may represent a funding source. Outcome databases should remain vigilant for the innovative and collaborative research opportunities to utilize or expand the database to secure new funding opportunities.

Quality Assurance and CQI These concepts are fundamental for generating high-quality, accurate, and reliable outcomes. Quality Assurance (QA) is the best way to determine process deviations and non-compliance. Quality transplant data has minimal unknowns or missing variables and acceptable levels of procedural deviations per regulatory requirements specified for transplant program. Periodic QA site visits and audits conducted by the regulatory authorities and accreditation bodies ensure compliance, safety, and optimal outcomes. The accreditation bodies for HSCT in the USA and Europe (FACT, JACIE, etc.) mandate that transplant centers collect and utilize standard core dataset defined by the field to analyze and understand their program quality. The built-in internal and external audit process for continuous quality improvement (CQI) is one of the best practices [11]. Quality maintenance of an HSCT center warrants added personnel, IT support, strategic, and risk communication. Quality management in HSCT can optimize survival outcomes by improving transplant practices.

Conclusion

HSCT has emerged as a definitive treatment for a myriad of inherited and acquired hematological malignancies and solid tumors. Data management is a core competency and one of the crucial components of the HSCT program that encompasses initiating and maintaining an institutional transplant database to augment data collection, analysis, and spearheading the research. There is a growing need to adopt the best data management practices for high-quality transplant data infrastructure to determine trends for QI and the most advanced therapeutic option to optimize health outcomes (engrafting, toxicity, and survival outcome) and benchmarking. Accredited and standardized databases can provide highly valuable information and research data that cannot be obtained by other research methodologies. Existing international models are an excellent resource for adopting best practices in maintaining data management with advanced standards and capabilities. The standardization of data quality is critical to ascertain the scientific credibility and function of outcome registries. The World Health Organization (WHO) recommendation to mandate data collection on guiding principles on cell, tissue, and organ transplantation has been a significant new development. The data collection and analysis would be an integral part of therapy and an obligation rather than a choice for transplant centers and will be a requirement for HSCT program accreditation. The program data standardization is vital to ascertain the scientific credibility and reliability of a transplant program.

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