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Pharmacovigilance and Epidemiology Department
Inspections, Human Medicines, Pharmacovigilance and Committees Division

CAR T-cell therapy Registries Workshop

Appendix 1: Proposed data elements relating to Efficacy and to Safety

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Table 3. Proposed data elements relating to Efficacy, priority for collection, current capture in registries and participant comments

Topics	Data	Priority for collection in Registry	Already captured by the Registries?	Comments from Workshop
Demographics	Age, Gender, Height, Weight, Centre	Crucial	Yes	Collected
Information on the malignancy	Documented diagnosis using a standard terminology (Read, ICD, other)	Crucial	Yes	Variable definition and details across centres and countries; Need agreed common definitions to permit outcome comparisons. EBMT uses WHO definition system for haematological malignancies CIBMTR: WHO system currently undergoing implementation
	Date of Diagnosis	Crucial	Yes	Date of definitive diagnosis using histology, molecular, cyto-genetic methods
	Disease burden / stage at cellular therapy treatment	Crucial	Yes	Recorded at the date of treatment – this is a likely outcome effect modifier
Functional status / Prognostic information	Performance status	Crucial	Yes	Both registries collect Karnofsky performance status and Comorbidities Index information
Prior therapy for the malignancy	Lines of therapies	Crucial	Yes	Captured, but therapies differ between centres & countries & there is no definition of what constitutes a 'line of therapy'. EBMT suggests product name plus start & end dates for all therapies should be sufficient. CIBMTR suggests two-tier determination: up-front v relapsed / progressed disease therapy
CAR T-cell administration	Product and dose	Crucial	Yes	Registries note that details are captured along with the product information – implicit in name of product

Table colour Key

Mainly once-only data items for entry to the registry	Data items requiring on-going / long term entry to the registry

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Topics	Data	Priority for collection in Registry	Already captured by the Registries?	Comments from Workshop
CAR T-cell Early Response: Efficacy measures & assessment	Treatments for side effects (e.g. cytokine release syndrome, CRS)	Crucial	EBMT: No	Feasible (Also a safety measure); Suggestion to collect treatment information only for CRS as this will inform severity grading. There is currently no standard grading system for CRS. Dosing detail may be too complex to collect in detail, e.g., tapering steroid doses
	Response: objective response rate, duration of response, relapse free survival, event free survival	Crucial	Yes	General agreement that review at 6 months would be sufficient with retrospective review of status at 3 months undertaken if there was disease progression at 6 months. Suggested by some participants that 1) Response criteria should be harmonised (eg. NCI criteria v Lugano for NHL); 2) MRD negative rates should be captured, especially for ALL where MRD testing is available. Noted that response criteria are likely to change over time
Later Response: Efficacy events	Response: yearly assessment (objective response rate, duration of response, relapse free survival, event free survival)	Crucial	Yes	Agreement on yearly collection
Follow up: Efficacy	Is the patient still alive? (Y/N) If no, specify date of death and cause	Crucial	Yes	Already captured
	Last known alive date	Crucial	Yes	Already captured
	New morbidity or malignancy diagnoses - date, type	Crucial	Yes	EBMT captures the diagnosis and the date of diagnosis CIBMTR captures diagnosis, date of diagnosis, location, histologic type Participant suggestion to use ICD coding for diagnosis
	Next malignancy treatment (type), if any, including stem cell transplant	Crucial	Yes	EBMT: if next treatment is stem cell transplant or cellular therapy, it is already captured.
	Relapse free survival & Event-free survival	Crucial	Yes	Already captured

Topics	Data	Priority for collection in Registry	Already captured by the Registries?	Comments from Workshop
Early & later Response: Efficacy measures	Health technology assessment (HTA) perspective on measures that will constitute early and later efficacy	Should have	Quality of Life (QoL) measures not currently collected	Suggested that HTA-relevant measures in the early response phase are generally likely to be the same as many of the preceding 'crucial' measures; CIBMTR suggested that 'time/date of next line of therapy' would also be HTA-relevant Burden of collection of other measure mentioned; Generic or disease-specific HRQoLs were also mentioned, eg EQ5D, SF36, QLQ-C30 (-MY20), FACT-G (-LYM) EBMT does not currently collect QoL measures
Follow up: Efficacy	Subsequent anti-cancer treatments given [Name/s, start/end date, response evaluation for each therapy]	Should have	EBMT already collects SCT	EBMT & CIBMTR noted the data should be basic owing to collection burden; Some MAHs/MAAs suggested the information was relevant for safety measures and 'should be collected' but did not remark on detail

Topics	Data	Priority for collection in Registry	Already captured by the Registries?	Comments from Workshop
Demographics	Ethnicity	Nice to have	No	Collection dependent on region – collection not universally permitted; EBMT & CIBMTR note difficulties in collection
	Human leucocyte antigen (HLA, product specific)	Nice to have	No	EBMT collects this information for allografts; CIBMTR noted this is applicable to 'off the shelf' CAR products which need HLA information for optimal product selection; collection will become increasingly complex for next-generation sequencing.
Prior therapy for the malignancy	Prior stem cell transplant	Nice to have	Yes	Type and date of transplant information is collected
Current malignancy treatments	Names, doses, frequency, duration (start/end dates)	Nice to have	EBMT: Names, doses, start & end dates	Participants noted complexity of capturing detail; CIBMTR suggest collection of number of prior lines of therapy; MAHs/MAAs suggested frequently used regimens could be defined and indicated by tick-box
Co-morbidities / Medical History	List of existing co-morbidities, severity as applicable - Hepatitis B, C; HIV; Active CNS problems	Nice to have	No	CIBMTR suggest use of standardized co-morbidity indices (Sorror 2013*; Charlson Comorbidity Index); MAHs/MAAs suggested Sorror also & noted that renal & hepatic indices are needed for patients with impairments; EBMT suggests a selection list of relevant conditions could be helpful
Co-morbidity treatments & other current treatments	Names, doses, frequency, duration (start/end dates), interactions with other products	Nice to have	No	EBMT noted this could be done but would involve a high clinician work burden
CAR T-cell therapy clinical trial participation	Yes / No	Nice to have	Yes	EBMT noted this is already recorded at centre-level but centres must be willing (i.e. permitted under trial rules) to share the information with EBMT; CIBMTR: records trial participation
	If No, list the exclusion criteria applying to the patient	Nice to have	No	Workshop participants considered 'no' in relation to 'clinical trial participation' to be sufficient information
CAR T-Cell Administration	Lymphodepleting chemotherapy: agents, date/s of administration, product, dose, batch number, reconstitution procedures	Nice to have	Yes	EBMT noted agents, date/s of administration, product, dose, batch number, reconstitution procedures could feasibly be collected
	Methodologies used to measure CAR T-cells expansion and persistence	Nice to have	No	Currently not feasible; CIBMTR also noted that no PK assays are available currently

Topics	Data	Priority for collection in Registry	Already captured by the Registries?	Comments from Workshop
Allergies	Allergies: None or specify	Not needed	No	Broadly considered as not needed; CIBMTR noted this is 'a moving target'
Information on the malignancy	Diagnosis confirmed by (method - biopsy etc.)	Not needed	No	Registries considered not needed. MAHs/MAAs variable – one considered not needed, one considered 'valuable information' (eg, % blasts in bone marrow for ALL)
CAR T-Cell Administration	Target Antigen/and its tissues distribution/oncongen adherence and surface density, transmembrane domain and costimulatory domain	Not needed	No	Registries considered not needed; CIBMTR noted target antigen is implicit with product; MAH/MAA noted the information was 'too complex for a registry'
	Gene transfer method	Not needed	Yes (EBMT)	Both registries considered not needed though EBMT noted the information was collected; CIBMTR and MAHs/MAAs noted this is included in product characteristics
	Risk of insertional oncogenesis (e.g. Vector design, Insertion profile, Vector dose, Transgene product, Target cell population)	Not needed	No	CIBMTR noted this needs lab assessment & would be available from centres; MAHs/MAAs considered this part of product characteristics
	Risk of contamination: Care givers, close contacts, risk to the environment	Not needed	No	No comments
	Transduction efficiency of the (target) cells (% of CAR+ cells)	Not needed	Yes (EBMT)	Considered not feasible for routine clinical care; MAHs/MAAs considered this a 'research question'

* Sorror ML. Blood 2013; 121:2854-63. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624933/

Topics	Data	Priority for collection in Registry	Already captured by the Registries?	Comments from Workshop
Early Response: Efficacy measures	Virus integration profile and clonal analysis of the circulating T-cells	Not needed	No	Considered not feasible in routine clinical care
	Duration and extent of B-cell depletion	Not needed	No	Registries & MAHs/MAAs noted that intravenous immunoglobulin use/need would provide an indirect measure
	Persistence of the CAR T-cells in the body	Not needed	No	Not available
	Minimal residual disease (MRD)	Not needed	Yes (EBMT)	CIBMTR noted this is disease-specific; could be considered for ALL but challenging; MAHs/MAAs considered should be feasible in ALL
Later Response: Efficacy events	Any sequelae of early complications of the treatment (CRS, infections etc.)	Not needed	No	Some participants noted this would be captured through adverse event evaluation
	Growth / development progress & milestones (Child)	Not needed	No	EBMT considered not needed; CIBMTR noted the data could be collected; MAHs/MAAs variably considered not needed or considered that 'registry should have the option to capture this'
	Relevant laboratory parameters	Not needed	No	EBMT to check if lab data are collected; CIBMTR noted that desired lab parameters need to be defined & need to know if these are collected in 'routine practice' or not. MAHs/MAAs variably considered not needed or considered that 'registries should have the option to collect'

Table 4. Proposed data elements relating to Safety, priority for collection, current capture in registries and participant comments

Topics	Data	Priority for collection in Registry	Already captured by the Registries?	Comments from Workshop participants
Early Response-Safety	Drug-related adverse events: neurological events (incl. cerebral oedema), cytokine release syndrome (CRS)/ macrophage activation syndrome (MAS), cytopaenias (bone marrow recovery), tumour lysis syndrome (TLS), certain infections (eg, sepsis, Hep B reactivation)	Crucial	Yes	Grading criteria for these AEs are not consistent across sites/registries, eg, no agreed grading system for CRS. Hence, suggestion that clinical details of associated symptoms, signs, severity are needed for CRS/ MAS/ TLS/ neurological/ life-threatening infections. Registries currently record if the events occurred - CIBMTR noted that AE information needs to be routinely recorded in medical records if detail is to be captured; CIBMTR does not record TLS; EBMT noted data burden for centres if clinical detail on each AE is to be included. MAHs/MAAs note that workshop participants agreed Yes/No sufficient for TLS, suggest MedRA terms be used, agree Grade 1, 2 severity events would be excluded, and support use of 'well-accepted grading systems' where possible.
	Drug-related (grade 3-4) adverse events: skin; respiratory, cardiovascular, hepatic, renal, gastrointestinal, other system events; Duration of B-cell aplasia/ hypogammaglobulinemia;	Crucial	Yes	Grading for these AEs is sufficient but need to ensure centres / registries use a consistent grading system; EBMT noted that to ensure consistent grading across centres contributing data, training will be needed; CIBMTR noted most toxicities are captured at Grade 4 level; MAHs/MAAs nominated grade 3 or higher, suggested CTCAE system, and one suggested hypogammaglobulinaemia as a surrogate for B cell aplasia 'which is not standardised in terms of management or measurement'.
	Treatments for any of the above	Crucial	Yes for some AEs	EBMT noted that it does not capture treatment for most AEs; high data burden for centres if all treatment details are to be captured; CIBMTR noted that 'only key elements' of any treatments should be collected, e.g., drug name only sufficient, not dose/duration & should restrict to events likely to be treatment-related; exclude others, e.g., hypertension, diabetes; MAHs/MAAs noted treatment name collected by CIBMTR;

Table colour Key

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Topics	Data	Priority for collection in Registry	Already captured by the Registries?	Comments from Workshop
Late Response - Safety	Safety assessment: months 3, 6, 12 and then yearly	Crucial	Yes	Participants asked if review at 6 months was sufficient with retrospective review of status at 3 months if there was a safety concern; EBMT noted preference to collect data at 3 months then annually but could do a 6-month review. CIBMTR noted that registry has 'calendar-driven data collection' but a 6-month review could still collect data from 3-months is necessary; MAHs/MAAs varied; tendency to prefer 3-month review.
	New malignancy; Insertional mutagenesis; New incidence or exacerbation of pre-existing neurological disorder; Hematological disorder; Hep B reactivation	Crucial	Yes (EBMT – malignancies only)	EBMT noted that diagnosis and date are currently collected; CIBMTR collects 'whether a new malignancy occurs, the histology, and whether there is evidence that the cells derive from the cell product'; pathology reports are requested but not always available; noted that biopsy on all new tumours is impractical & unnecessary for common solid tumours likely to be related to the cell therapy'. MAHs/MAAs varied but did not feel that biopsies were needed in all cases. If not routinely collected, a requirement for registry collection would represent an intervention.
Follow up	Is the patient still alive? (Y/N) If no, specify date of death and cause of death	Crucial	Yes	No comments
	Last known alive date	Crucial	Yes	No comments
Later events - Safety	Pregnancies & outcomes, CAR T-cells in neonate, B cell aplasia in neonate	Crucial to capture all pregnancies. Nice to have pregnancy outcome	Yes, conception captured but no other information	EBMT made no additional comments; CIBMTR noted that capturing pregnancy outcomes is 'generally beyond registry scope but could be included' and that assessment of CAR T-cells in the neonate would need separate protocol and resources. MAHs/MAAs noted CAR-T persistence is not feasible to assess but that persistence of B cell aplasia could be evaluated at the centres.

Topics	Data	Priority for collection in Registry	Already captured by the Registries?	Comments from Workshop
Early Response- Safety	HTA Perspective on measures that will constitute early safety	Should have	No	HTAs considered information on morbidity, quality of life & patient's view to be crucial; EBMT noted possibility of data collection depends on what HTAs sought; CIBMTR noted that resources must be invested to capture QoL systematically & collection of information on a patient subset is probable best to begin; need to agree on uniform assessment tools; MAHs/MAAs felt that some efficacy outcomes would inform HTA; noted that addition of QoL would be considered an intervention Use a standard QoL questionnaire.
Late Response - Safety	Development of GVHD, PML, rheumatological or autoimmune disorders; Other system disorders	Nice to have	Yes	EBMT collects GvHD and 'a series of complications' and noted a standardised (MedRA) list of codes should be suggested; CIBMTR captures GvHD (individual organ stage); date of onset of Grade 4 toxicities in other organs; noted that for other information, data fields would need agreement across registries. MAHs/MAAs noted these events would be captured via AE or SAE reporting
	Ongoing treatments for co-morbidities: Names, doses, frequency, duration (Start_End dates)	Nice to have	No (EBMT)	EBMT does not capture co-morbidity treatments & noted associated data burden; CIBMTR noted data burden & recommended only treatments for therapy-associated events (eg CRS) to be collected. MAHs/MAAs noted baseline hepatic & renal function should be collected 'as a crucial data element' at baseline & that 'MAH has received health authority request to assess CAR-T therapy in patients with hepatic and renal impairment within registry'.
	HTA Perspective on measures that will constitute later safety	Nice to have	No	EBMT does not collect measures currently; CIBMTR noted that considering the numbers that may receive treatment & since 'most toxicities seem to be short-term', QoL information collection may be impractical & suggested 'an electronic PRO instrument could be developed for a subset of patients'; MAHs/MAAs noted patient diaries would not permit standardised QoL data collection & that interpretation of data could be challenging; standard questionnaires might assist. Regulators noted that a patient diary was likely to be too heterogeneous to permit data extraction and queried whether collection of PROs is an intervention
Follow up	Persistence of CAR T-cells	Nice to have	Yes (EBMT)	EBMT noted data collected; CIBMTR & MAHs/MAAs made no comment; Regulators noted this was potentially valuable information but that data collection would be challenging in a registry and likely more suited to a follow-up extension study
	Quality of life (EQ5D, HRQoL) / Performance status	Nice to have	Yes (at baseline)	EBMT & CIBMTR currently capture at baseline only. MAHs/MAAs noted standard questionnaires would be needed. Regulators noted that standard questionnaires are used in some registries (*PMcG cross check given earlier point on interventional study*)
Later events - Safety	Pregnancies & outcomes, CAR T-cells in neonate, B cell aplasia in neonate	Crucial to capture all pregnancies. Nice to have pregnancy outcome	Conception only captured	See efficacy Table