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Evidence Check

CAR T-cell therapy: a summary of evidence

An **Evidence Check** rapid review brokered by the Sax Institute for the NSW Ministry of Health. November 2018.

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This report was prepared by:

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November 2018.

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Suggested Citation:

Kew K, Knight K, Karner C and Edwards S J. CAR T-cell therapy: a summary of evidence: an Evidence Check rapid review brokered by the Sax Institute (www.saxinstitute.org.au) for the NSW Ministry of Health, 2018.

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Contents

NSW Health recommendation: Given the uncertainty around the benefits, risks and high cost, NSW Health recommends cellular therapies **only** be provided to patients under a clinical trials framework until more substantive evidence is available.

CAR T-cell therapy: a summary of evidence was commissioned by the NSW Ministry of Health in response to increasing interest and activity in the area of cellular immunotherapies for cancer treatment. The report provides a summary of available evidence for CAR T-cell therapies, a review of current regulatory status and an in-depth horizon scan of clinical trials.

The report highlighted some important considerations for public investment in CAR T-cell therapies including the following:

- There is considerable uncertainty around the long-term benefits and risks of available CAR T-cell treatments. Clinical trials are limited by small populations with no long-term follow-up yet available.
- The average response rate achieved in clinical trials is 60%; however, it is currently unclear whether this therapeutic effect is maintained over time.
- Severe adverse events are common, affecting up to 40% of patients, some of which life are threatening. In addition, the risk of delayed onset toxicity is unknown.
- The evidence base is likely to evolve rapidly over the next few years. Internationally, there are over 250 clinical trials underway or planned.
- Current regulatory frameworks governing the introduction of new health technologies are being challenged by these therapies, both nationally and internationally, and specialist designations and support schemes are likely to be required to support their use.

November 2018

Glossary

Term	Definition
Allogeneic CAR T-cell therapy	Treatment that is manufactured from the T-cells of an external donor
Autologous CAR T-cell therapy	Treatment that is manufactured from the recipient patient's own T-cells
Complete remission	Tests, physical exams and scans reveal no signs of cancer
Grey literature	Material that is not listed in electronic bibliographic databases
ICER	Incremental cost-effectiveness ratio: the difference in cost between two possible interventions, divided by the difference in their effect
Intention-to-treat	Analysis based on all patients randomised or included in a study, regardless of noncompliance or withdrawal, etc.
Leukapheresis	Laboratory procedure in which white blood cells are separated from a sample of blood
Overall response rate	Proportion of patients with a predefined reduction in tumour burden, or complete remission
Progression- or event-free survival rate	Proportion of patients alive and whose cancer has not progressed at a given timepoint
QALY	Quality-adjusted life-year: measure of health in which survival benefits are adjusted to reflect quality of life
Relapsed or refractory	Cancer that has not responded, or has returned after previous treatment
Specialist designation	Regulatory processes that have been adapted to fast-track the approval process

Executive summary

Background / Purpose of the review

Chimeric antigen receptor (CAR) T-cell therapy is being hailed as the next generation of immunotherapy for the treatment of cancer. CAR T-cell therapy harnesses the immune system to attack cancerous cells. The treatment is manufactured individually for each patient by extracting T-cells from the patient's own blood (autologous) or from a healthy person (allogeneic). The T-cells are genetically engineered to allow the immune system to detect and kill cancerous cells when transplanted back into the patient. The development of allogeneic CAR T-cell therapies from donors may offer a faster and cheaper alternative to the autologous therapies approved thus far.

Promising results have been seen for CAR T-cell therapy as a treatment for leukaemia and lymphoma, which has led to accelerated regulatory approvals and rapid proliferation of trials developing CAR T-cell therapies for a range of other cancers. Unprecedented response rates have been reported, although the durability of response is unknown, and serious safety issues have been identified. Manufacturers, research bodies and regulators are considering how best to assess the long-term efficacy and safety of CAR T-cell therapy within existing systems to ensure patients have safe access to potentially life-saving treatments as soon as possible.

This Evidence Check was commissioned by NSW Health to provide a summary of the available evidence to inform future health technology assessments of CAR T-cell therapy.

Review questions

This review aimed to address the following questions:

Question 1: What regulatory frameworks are in place, or under consideration, for the delivery of CAR T-cell therapy?

Question 2: Where CAR T-cell therapies have been approved and are delivered within a regulatory framework, what is the evidence for the safety, efficacy and cost of these therapies?

Question 3: What clinical trials have been conducted or are underway for CAR T-cell therapy?

Summary of methods

The reviewers searched Medline, Embase and the Cochrane Library for publications relevant to one or more research questions that were published between 2015 and July 2018 (n = 3028 after duplicates removed). ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform were searched for clinical trials of CAR T-cell therapy (n = 467 after duplicates removed). Registry searches were not limited by study design (e.g. randomised or single arm), study Phase (I, II, III or IV), or recruitment status. We conducted grey literature searches through OpenGrey.eu (formerly SIGLE) and websites of international health technology assessment (HTA) bodies and regulatory agencies (n = 102), manufacturers of CAR T-cell therapy (n = 29), and universities and non-commercial organisations engaged in CAR T-cell research (n = 33). All searches were limited to human research published in English from 2015 onwards.

One reviewer conducted a title and abstract sift of all records, and 20% of records were reviewed independently by a second reviewer. Evidence of CAR T-cell therapy for cancer was of interest, but we noted clinical trials in non-cancer indications. Potentially relevant records were reviewed in more detail for inclusion and assigned to one or more research questions. Discrepancies were resolved through discussion,

or by consulting the full text. Information was extracted about planned or implemented regulatory frameworks (including service delivery models, access and funding models) for research question 1, completed or planned post-authorisation studies for research question 2, and clinical trials for research question 3.

There were 350 relevant records from the peer review literature, 377 from clinical trials registries and 30 from grey literature searches assigned to the research questions. The literature selection process is detailed in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Evidence grading

Evidence for research question 1 was not graded because it constituted narrative information retrieved from websites and policy reports. The quality of evidence retrieved for question 2 was graded according to the National Health and Medical Research Council (NHMRC) levels of evidence[1], and biases were considered across ongoing trials for question 3.

Key findings

Question 1:

For question 1, we included 47 key evidence sources describing 17 regulatory frameworks and approvals. Characteristics of regulatory approvals were tabulated and details of regulatory frameworks summarised narratively.

Tisagenlecleucel (Kymriah®, Novartis) was approved by the US Food and Drug Administration (FDA) in August 2017 for adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and for patients aged under 25 years with relapsed or refractory B-cell acute lymphoblastic leukaemia (B-ALL). Axicabtagene ciloleucel (Yescarta®, Kite Pharma Incorporated) was approved by the FDA for the same adult DLBCL indication in October 2017, and the European Medicines Agency (EMA) recommended that marketing authorisations be granted for the same treatments and indications in June 2018. In Britain, an agreement has been reached for tisagenlecleucel to be provided through the Cancer Drugs Fund (CDF) for refractory paediatric B-ALL, and a decision for its use in adult DLBCL is pending; axicabtagene ciloleucel has received an initial negative recommendation but the decision was under consultation at the time of writing.[2-4] The CDF was set up to allow fast-track access to promising new treatments via managed access arrangements while further evidence was collected to address clinical uncertainty. Further CAR T-cell therapies are in the EMA and FDA pipelines, and those of agencies in Australia, China, Japan and Canada.

There is inconsistency in how CAR T-cell therapies are categorised by regulatory agencies, but various FDA–EMA initiatives have been set up to align their processes. The EMA categorises CAR T-cell therapies as a gene therapy under the category of advanced therapy medicinal products (ATMP), which are assessed by a specialist Committee for Advanced Therapies (CAT); and the FDA categorises them as a regenerative medicinal therapy to be assessed by the FDA's Center for Biologics Evaluation and Research (CBER) via the Office of Cellular, Tissue and Gene Therapies (OCTGT). The EMA and FDA have both outlined comprehensive plans for post-authorisation monitoring of CAR T-cell therapy and risk mitigation.

The EMA and FDA have acknowledged important challenges associated with CAR T-cell therapies that require an adapted regulatory approach: unique, complex and delayed safety issues; extremely high cost (US$350,000 to US$500,000); length of time taken to produce and ship the therapies; access issues (e.g. due to the location of specialist facilities); difficulty ensuring purity and potency due to individual manufacturing procedures; and early stage, single-arm trials in small populations. Tisagenlecleucel and axicabtagene ciloleucel were the first treatments considered eligible for the EMA's specialist Priority Medicines (PRIME) scheme, which provides early dialogue and support for manufacturers of promising therapies. Similarly, the treatments were eligible for the FDA's breakthrough therapies designation. It is acknowledged that

simplifications to regulatory processes, such as those employed by the EMA and FDA, are required to ensure safe and timely access to promising CAR T-cell therapies.

HTA agencies have so far considered existing processes suitable for CAR T-cell therapies (Britain's National Institute for Health and Care excellence [NICE] and the Canadian Agency for Drugs and Technology in Health [CADTH]), but there are challenges posed by multiple indications, small single-arm studies with short follow-up, unconfirmed pricing and resource requirements (e.g. for managing novel toxicities), and poorly defined comparators. Proposed solutions across key evidence sources include: early and continued dialogue between manufacturers, regulators and payers; incorporation of real-world evidence for initial risk–benefit assessments; horizon scanning by reimbursement and HTA bodies; collaboration with patients, clinical experts and implementation groups; and development of innovative payment agreements to manage uncertainty.

Question 2:

For question 2, reviewers identified 19 key evidence sources including nine systematic reviews[5-13] (three incorporating economic analyses[5, 7, 10]), five post-authorisation studies, and regulatory presentations and guidelines.[14-18] There is currently no randomised, long-term evidence or real-world data for CAR T-cell therapy because of the length of time treatments have been available outside of clinical trials. Meta-analyses and comparative cost-effectiveness analyses are only available for B-cell haematological malignancies and are based on small single-arm trials with limited follow-up. Comprehensive post-authorisation monitoring plans have been put in place by the EMA and FDA but are in their infancy. The evidence is therefore considered Grade III–3.[1]

Substantial efficacy benefits of CAR T-cell therapy for B-cell malignancies are noted in systematic reviews of multiple indications: the average response rate is about 60% and results suggest CAR T-cell therapy may be most effective for ALL (75–93% response), followed by chronic lymphocytic leukaemia, or CLL (54–62% response) and non-Hodgkin's lymphoma, or NHL (36–39% response). Complete remission (CR) across conditions was achieved in between 15% and 20% of patients. PFS varied, but approximately 43–50% of patients were progression-free at six months, and 18–27% were progression-free at one year.

Cost-effectiveness analyses based on naive indirect treatment comparisons (i.e. direct comparison of single arms from different studies) indicate CAR T-cell therapies may have meaningful benefits over alternative treatments for paediatric B-ALL and adult refractory lymphoma. Overall remission for paediatric B-ALL, based on a report by the Institute for Clinical and Economic Review (ICER), is from 57–73% for tisagenlecleucel based on the full population (69–95% 'per-protocol' when only those infused were included) and from 20–63% for clofarabine and blinatumomab. The difference between the full population and 'per-protocol' results means real-world efficacy is likely to be overestimated by systematic reviews based only on those who received treatment. The base-case incremental cost-effectiveness ratio (ICER) for tisagenlecleucel versus comparators was US$45,871 per quality-adjusted life-year (QALY) gained. ICER also assessed axicabtagene ciloleucel and tisagenlecleucel for the adult refractory lymphoma population, and both showed substantially higher efficacy than salvage chemotherapies: overall response rate (ORR) was 82% and 73% in the axicabtagene ciloleucel studies, 64% and 53% in the tisagenlecleucel studies, and 26% for salvage chemotherapies, and CR was 73% and 55% for axicabtagene ciloleucel, 57% and 40% for tisagenlecleucel, and 7% for salvage chemotherapies. A base-case ICER calculated for axicabtagene ciloleucel versus salvage chemotherapy was US$136,078 per QALY gained.

Severe adverse events of CAR T-cell therapy that have been highlighted consistently in trials and systematic reviews of B-cell haematological malignancies are: cytokine release syndrome (CRS), neurotoxicity, fever, encephalopathy, kidney injury, hypotension, hypoxia, headache, infections, dyspnoea, neutropenia and B-cell aplasia. A recent meta-analysis estimates 29% of those with B-ALL, 39% of those with B-CLL and 20% of those with B-NHL have experienced severe CRS after receiving CAR T-cell therapy, and another analysis

estimates more than 40% of patients have developed B-cell aplasia. Overall, wide confidence intervals around the pooled safety estimates reflect variability in observed rates and the uncertainty associated with small sample sizes. Key clinical uncertainties are noted, and cost-effectiveness was sensitive to the assumptions made, e.g. about pricing structure, long-term efficacy and treatment for adverse events (particularly long-term intravenous immunoglobulins for B-cell aplasia).

Several post-authorisation systems and risk mitigation strategies have been put in place following the EMA and FDA regulatory approvals, from which results are not yet available. The FDA has outlined Approved Risk Evaluation and Mitigation Strategies (REMS) and requested two 15-year observational studies of at least 1000 patients for tisagenlecleucel (B2401) and axicabtagene ciloleucel. The FDA is also piloting a clinical safety repository of trial data to inform future regulatory reviews. The EMA has outlined plans for non-interventional post-authorisation safety and efficacy studies for axicabtagene ciloleucel and tisagenlecleucel and requires periodic safety update reports until 2038. The EMA is also investigating ways of certifying, harmonising and auditing existing patient registries in the EU and US to support benefit–risk evaluations and post-authorisation monitoring of CAR T-cell therapies.

Question 3:

Trial publications and information from the grey literature were matched to clinical trials registry records, which gave a list of 390 unique clinical trials for a range of cancers and 212 unlinked records (study details available in supplementary Microsoft Excel® file). We acknowledge that many CAR T-cell therapy trials are being conducted by non-commercial teams that may not all be documented on a clinical trial platform, meaning the number and nature of the trials landscape is difficult to capture accurately.

Most studies are listed as recruiting or enrolling by invitation (n = 267), 28 are not yet recruiting, five are authorised, 10 have been terminated or withdrawn and four have unknown status. Completed trials of CAR T-cell therapies for cancer are all Phase I or Phase II single-arm, unrandomised and open-label. Summaries and comparisons of the results of completed trials are difficult to make due to the rapidly growing and evolving evidence base, which covers a huge variety of populations, tumour targets, doses, manufacturing methods and outcome measures. Results of recent systematic reviews of CAR T-cell therapy for B-cell malignancies are summarised under research question 2.

Key observations of ongoing and completed clinical trials are:

- B-cell and haematological malignancies currently dominate the trial landscape; there are at least 140 trials of leukaemias (including ALL, CLL and acute myeloid leukaemia), 140 of lymphomas (including Hodgkin's and non-Hodgkin's lymphomas) and 36 of multiple myeloma
- Trials are mostly small and non-comparative; 275/390 have a target population of less than 50
- Trials are in progress for a range of solid tumours including renal cell carcinoma, pancreatic and pleural adenocarcinoma, glioblastoma, neuroblastoma, and gastric, thyroid, ovarian and breast cancers
- Most trials are being conducted in the US, but many are underway around the world, including in China, Europe, Japan and Australia
- In Australia, recruitment is underway or starting soon for international trials in adult and paediatric aggressive lymphoma, low-grade lymphoma and relapsed ALL (all with off-site manufacturing). An Australian early stage Phase I trial with local manufacturing is also underway in solid cancers, and a trial for myeloma is in the preclinical phase
- CD19 is the most common target but numerous others are being studied (notably CD20, CD22, Igk and B-cell maturation protein BCMA); identifying successful target antigens for non-B-cell malignancies and solid tumours has proved challenging
- Most completed studies have used an autologous cell source (i.e. from the patient), but Phase I results are emerging for allogeneic CAR T-cell therapies (e.g. UCART19)

- Phase I trials are exploring strategies to reduce on-target/off-tumour autoreactivity of CAR T-cells towards healthy tissue, such as 'suicide genes' and safe dosing strategies
- Safety outcomes are listed consistently, but we noted variation across disease areas and methodologies for efficacy outcomes; commonly listed outcomes are rates of complete remission and overall response.

Gaps in the evidence

- Evidence for regulatory frameworks and HTA are limited to North America and Europe and may not be applicable to other health systems
- Post-authorisation studies are in the early stages and most have not yet reported results
- Clinical trials of CAR T-cell therapies are currently limited to single-arm, open label, Phase I and II studies with short follow-up, which poses challenges for the assessment of treatment durability and long-term safety.

Discussion of key findings

Comprehensive and systematic searches identified international evidence including peer-reviewed articles, systematic reviews, regulatory and governmental reports and HTAs. We extracted and synthesised evidence to provide an overview of the regulatory challenges posed by CAR T-cell therapies and proposed approaches to ensure patients with relapsed or refractory cancers have safe access to promising treatments.

Existing regulatory frameworks for advanced and regenerative medicines have been applied successfully to two autologous CAR T-therapies in the European Union and US. Further CAR T-cell therapies are making their way through EMA and FDA pipelines (Europe and US), and progress is being made in Australia, Canada, China and Japan. The experiences of the FDA and EMA suggest the regulation of CAR T-cell therapies internationally will benefit from employing specialist designations and support schemes, and collaboration in the generation of centralised datasets and repositories to support risk–benefit analysis.

Evidence syntheses to provide overviews of the efficacy, safety and cost-effectiveness of CAR T-cell therapies are currently limited by the size and single-arm design of early stage trials, and variation between them. Overall, systematic reviews indicate substantial health benefits of autologous CAR T-cell therapies (primarily tisagenlecleucel and axicabtagene ciloleucel), with overall response ranging from 36–93% in systematic reviews of CAR T-cell therapy for different B-cell haematological malignancies; results appear most promising for paediatric B-ALL, while early results in other cancers are less favourable, particularly in solid tumours. Results based on full intention-to-treat populations are less favourable than those based only on patients who received treatment, and the latter may overestimate real-world effectiveness. Limited follow-up means the durability of treatment effects is unknown, which has implications for the assessment of cost-effectiveness. Adverse events are common and can be life-threatening, the risk of delayed onset toxicity remains unknown, and there is substantial uncertainty in estimates of comparative effectiveness. Research is focusing on strategies to reduce and manage toxicity and, while risk mitigation strategies mandated by the FDA and EMA are in their infancy, coordinated initiatives are in place to capture long-term data as CAR T-cell therapies are implemented.

Local payers conducting implementation assessments should acknowledge the costs of building and operating new specialist manufacturing facilities, and/or the time and infrastructure required to manufacture and ship CAR T-cell therapies from existing facilities, and the training of specialist staff to manage novel toxicities. There is a precedent for outcomes-based payment in the US, which may inform discussions for future therapies to mitigate uncertainty until more mature data can be supplied and comparative assessments made.

Implications for Australia

Australia is likely to encounter similar issues in the assessment of CAR T-cell therapies as the countries and regions where they have already been assessed and approved, such as the limits of the evidence base and complex and potentially long-term safety issues. Factors to be considered on a local and national basis for the assessment and implementation of CAR T-cell therapy in Australia include:

- Strategies to manage uncertainties in long-term risks and benefits, such as outcomes-based pricing agreements to offset high upfront costs
- Costs of specialist manufacturing resources, accredited facilities and specialist training to deliver CAR T-cell therapy and manage novel toxicities
- Regulatory support and possible discounts for small enterprises and non-commercial bodies submitting marketing applications for CAR T-cell therapies
- Suitability of existing clinical trials guidelines, manufacturing legislation and regulatory and HTA processes for CAR T-cell therapy
- The location of facilities to ensure equality of access and timely, quality-assured manufacture; Australia currently has no accredited sites, but existing sites that are good manufacturing process (GMP) compliant could be accredited to manufacture CAR T-cells
- Development and implementation of a risk-evaluation and mitigation strategy.

Conclusion

The speed with which the research into CAR T-cell therapy and other gene therapies has progressed is reflected in the proliferation of peer-reviewed research, guidelines and regulatory documents found in this Evidence Check. Countries where CAR T-cell therapy has yet to be approved can learn from the experiences of agencies that have adapted processes and found initiatives to cope with the challenges posed by the wide range of CAR T-cell therapies coming through the pipeline.

Background

Chimeric antigen receptor T-cell therapy (CAR T-cell therapy) is being hailed as the next generation of immunotherapy for the treatment of cancer. It is a form of gene therapy designed to harness the patient's immune system to identify and attack cancerous cells. Most CAR T-cell therapies are manufactured individually for each patient (autologous CAR T-cells) by first extracting T-cells (white blood cells) in a process called leukapheresis. The extracted T-cells are then shipped to be engineered in a laboratory to express a receptor for components of tumour cells, allowing the immune system to detect and kill cancerous cells when the T-cells are transplanted back into the patient. Autologous CAR T-cell therapies require T-cells from the patient's own blood and are associated with significant cost; however, research is underway to develop cheaper and more practical 'off the shelf' allogeneic CAR T-cell products that can be manufactured in advance to be stored and shipped as required.

CAR T-cell therapy has shown most promise in the treatment of relapsed or refractory B-cell haematological cancers: acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL). The treatments offer the potential of a cure and there have been high initial response rates observed in regulatory trials.[19] However, preclinical and early clinical trials suggest the benefits seen in blood cancers are difficult to replicate in solid tumours[20], and serious complications have included life-threatening fevers and hypotension due to cytokine release syndrome (CRS). Advances continue to be made in improving the safety and efficacy of CAR T-cell therapies, including modifications that allow the CAR T-cells to switch off should toxicity occur (so-called 'suicide genes'). Nonetheless, there remain unanswered questions about the durability of response and the therapies' long-term safety, including the possibility of secondary malignancies.

Tisagenlecleucel (Kymriah, Novartis) and axicabtagene ciloleucel (Yescarta, Kite Pharma) are the first two CAR T-cell therapies to be granted regulatory approval for patients with ALL and DLBCL. Promising results during their clinical development led to the rapid proliferation of research to develop and test CAR T-cell therapies for a range of other cancers, for which there are hundreds of trials in progress. The large number of therapies and indications, mostly being tested in small populations, is creating novel challenges for regulators to overcome in ensuring the safety and efficacy of treatments for use in clinical practice. Regulators and policy makers are considering ways of adapting process to prevent bottlenecks in existing approval systems and ensure patients have safe and timely access to potentially life-saving treatments.

The first CAR T-cell therapies have been approved through accelerated approval systems for promising treatments in North America and Europe, and there are currently no regulatory approvals in Australia. This review was commissioned by NSW Health to provide a summary of the available evidence to inform future health technology assessments (HTAs) of CAR T-cell therapy. The report findings may be used to inform policy and funding decisions in other jurisdictions, including by Council of Australian Governments (COAG) Health Council subcommittees and state/territory senior policy makers.

Methods

Scope of the review

The scope of this Evidence Check was to review and summarise available information to address three research questions:

Question 1: What regulatory frameworks are in place, or under consideration, for the delivery of CAR T-cell therapy?

Question 2: Where CAR T-cell therapies have been approved and are delivered within a regulatory framework, what is the evidence for the safety, efficacy and cost of these therapies?

Question 3: What clinical trials have been conducted or are underway for CAR T-cell therapy?

The review also sought to assess the level of evidence available for each research question, and to highlight gaps in the evidence base.

Literature searches

We conducted a variety of searches to identify peer-reviewed and grey literature about CAR T-cell therapy. Full search strategies for each database, as well as lists of grey literature sources reviewed, are provided in the Appendices.

Peer-reviewed literature

Medline, Embase and the Cochrane Library were searched in June 2018 for literature published from 2015. Search strategies combined MeSH descriptors for CAR T-cell therapy with those for cancer. Alternative terms for CAR T-cell therapy included product codes and brand names of approved CAR T-cell treatments (see Appendix 1), which were verified with clinical experts.

We sought international literature for countries with regulatory approval for CAR T-cell therapies, but included only those papers published in English. Evidence for all three research questions was sought in the peer-reviewed literature.

We combined and de-duplicated results from the three databases before sifting them using online software (https://rayyan.qcri.org/). One reviewer conducted a title and abstract sift of all records against predefined inclusion criteria, and 20% of records were reviewed independently by a second reviewer. We resolved discrepancies through discussion, or by consulting the full text. In a second sift, potentially relevant records were reviewed in more detail for inclusion and assigned to one or more of the research questions.

Clinical trials registries

We searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform using a range intervention terms (see Appendix 2). Searches were not limited by study design (e.g. randomised or single arm), study Phase (I, II, III or IV) or recruitment status, and no other population limits were used (e.g. size of cohort or age). Results were limited to those last updated from 2015. At the request of the commissioning agency, the search of ClinicalTrials.gov was not limited by condition to identify ongoing clinical trials in other disease areas, but the WHO search was limited to populations with cancer.

Results of the WHO search were cross-checked with results from ClinicalTrials.gov, and the remaining records were appraised independently by two reviewers in Excel for relevance to research question 3.

Grey literature

Website searches for grey literature combined a variety of terms to identify online material and documents that were not identified in the peer-reviewed literature or clinical trials registries. Relevant documents and web pages were collated from websites of international HTA and regulatory bodies, and information was subsequently extracted about planned or implemented regulatory frameworks, service delivery models, and access and funding models for research question 1. HTA body websites were also checked for information relevant to research questions 2 and 3. Websites of manufacturers, universities and non-commercial organisations engaged in CAR T-cell research were searched for completed or planned post-authorisation studies for research question 2, and for clinical trials for research question 3. Finally, OpenGrey.eu (formerly SIGLE) was searched for records relevant to any research question.

We searched websites using a range of intervention terms (see Appendix 3) or navigated manually where search functions were not available. Lists of relevant universities and non-commercial organisations were informed by clinical experts. All grey literature searches were limited to human research published in English.

Evidence grading

Given that evidence sought for research question 1 constituted primarily narrative information retrieved from websites and policy reports, it was not appropriate to conduct critical appraisal or assess the grade of evidence. The overall level of evidence retrieved for question 2 was graded according to the National Health and Medical Research Council (NHMRC).[1]

Study results were not available for most clinical trials identified for question 3, so it was not possible to critically appraise the trials according to domains of the Cochrane Risk of Bias tool as planned. Alternatively, potential bias associated with study design — such as blinding and group allocation — was summarised narratively across completed, ongoing and planned studies.

Included studies

The literature selection process is detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the literature selection process in Appendix 4.

Searches of the peer-reviewed literature returned 3751 records, of which 723 were identified as duplicates and removed. Of the remaining 3028 records, 2096 were excluded in the initial sift. After reviewing 932 records more closely, 350 were considered relevant and assigned to the research questions.

Information was extracted from the peer-reviewed literature and documents retrieved and reviewed from 102 HTA websites, 29 company websites, 33 university and non-commercial websites and 543 results from OpenGrey.eu. Information and evidence from 30 key evidence sources from grey literature sources were included in the review. For question 1, we included 47 key evidence sources, which contained information about 17 regulatory frameworks and approvals.[2-4, 7, 15-18, 20-58] Characteristics of regulatory approvals are tabulated in Appendix 6, and details of regulatory frameworks are summarised narratively from policy documents and bulletins in the report text. For question 2, we identified 19 key evidence sources, including nine systematic reviews[5-13] (three incorporating economic analyses[5, 7, 10]) and five post-authorisation studies[33, 46, 53-55]; other sources of information were regulatory presentations and guidelines.[14-18] Study characteristics were extracted, tabulated and summarised narratively to address research question 2.

Searches of clinical trial registries returned 507 records. After identifying and removing 40 duplicates, we considered the remaining 467 for inclusion, and 377 met the inclusion criteria for research question 3. The unique registry identifiers were used to compile a list of clinical trials organised by stage of development (e.g. completed, active, recruiting, withdrawn). We added additional trials from the grey literature searches, giving a total of 390. Records assigned to research question 3 in the peer-reviewed literature search were linked to a clinical trial record where identifiers could be matched (n = 111). However, most reports from the

peer-reviewed literature did not provide sufficient information to link them with an existing record (n = 212), or to exclude the possibility of multiple records describing the same study.

Summary tables of evidence meeting criteria for research questions 1 and 2 are provided as Appendices 5 and 6, respectively. Due to the large number of studies identified for research question 3, results have been summarised narratively and the full list and extracted information provided in a supplementary Excel file.

Findings

Research Question 1: What regulatory frameworks are in place, or under consideration, for the delivery of CAR T-cell therapy?

Regulatory approvals

At the time of writing, regulatory approvals of two CAR T-cell therapies have been granted by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Health Canada (see Appendix 5). The US was the first to approve two CAR T-cell therapies for two indications: tisagenlecleucel (Kymriah, Novartis) received FDA approval in August 2017 for adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)[53] and for patients aged under 25 years with relapsed or refractory B-cell acute lymphoblastic leukaemia (B-ALL)[55], and axicabtagene ciloleucel (Yescarta, Kite Pharma) was approved for the same adult DLBCL indication two months later (October 2017).[54] The same two therapies for the same indications were recommended by the EMA in June 2018, and full EMA marketing authorisations granted in August.[33]

Sources retrieved in the search indicate that other CAR T-cell therapies are in the EMA and FDA pipelines, and that progress is being made to assess and implement CAR T-cell therapies in Australia, China, Japan and Canada[24, 25, 38], but no other approvals were noted. Potential future approvals are outlined in two horizon scanning reports for axicabtagene ciloleucel and tisagenlecleucel published in Britain by the National Institute for Health Research (NIHR)[43, 44] and a gene therapy bulletin by the Canadian Agency for Drugs and Technologies in Health (CADTH).[24] Indications for which axicabtagene ciloleucel has been granted orphan status, which may indicate future approvals, are mantle cell lymphoma (September 2015 EMA, May 2016 FDA); follicular lymphoma (November 2015 EMA, May 2016 FDA); chronic lymphocytic leukaemia (CLL) (November 2015 EMA, April 2016 FDA) and primary mediastinal B-cell lymphoma (FDA April 2016).[43]

Approval frameworks

Evidence identified in the searches indicates that the EMA and FDA frameworks have encountered similar issues in the assessment of CAR T-cell therapies.[16, 20, 21, 25, 32, 56] Both agencies, and the bodies that govern them, acknowledge that the unique characteristics of CAR T-cell therapies require an adapted approach to clinical trials and risk–benefit assessment for regulation.[32, 46] Important challenges found in key evidence sources were:

- Unique, complex and substantial safety issues related to the persistence of the treatment's biological activity in the immune system, which may emerge after trials end
- Length of time taken to manufacture the therapies (weeks or months), and the need to implement cell shipping and tracking systems to ensure safety[35, 40, 41]
- Consideration of factors affecting access, such as the location and coverage of facilities with sufficient expertise to deliver CAR T-cell therapy safely and manage toxicities[37, 40, 45]
- Difficulty ensuring purity and potency due to individual manufacturing procedures; it is noted that legislation and guidelines for gene therapies apply to CAR T-cell therapy[30, 31, 34, 35, 42, 47, 52]
- Large number of early stage, single-arm trials in small populations, and with short follow-up
- Lack of familiarity with regulatory processes for those developing the treatments (more often universities or non-commercial bodies rather than pharmaceutical companies).[32]

A report by CADTH looked at all medicines approved under a number of EMA, FDA and Health Canada special designations and indicated that CAR T-cell therapies have so far been eligible for the EMA's Priority Medicines (PRIME) scheme and the FDA's Breakthrough Designation.[20, 33, 43] Schemes such as PRIME

acknowledge that CAR T-cell therapies are frequently developed by small non-commercial organisations and universities that are unfamiliar with regulatory requirements and have fewer resources, and engage in early communications to improve the generation of evidence. Reports from the European Commission and the EMA suggest further simplifications to often cumbersome regulatory processes are required to make them easier to navigate for smaller companies, and to speed up access to advanced therapies.[29, 32] Other FDA regulatory routes for which CAR T-cell therapies may be eligible include Fast Track Designation and the Regenerative Medicine Advanced Therapy Designation.[56] Searches also highlighted that new regulations accelerating the approval of regenerative therapeutics in Japan took effect in 2014 and updated guidance for the assessment of gene therapies was due in early 2018, but we could find no additional information about the frameworks or progress.[27, 57] The Chinese Food and Drug Administration (CFDA) has also recently released Guiding Principles for the Research and Evaluation of Cell Therapy Products, which covers CAR T-cell therapy, to align China's drug regulations with global markets.[28]

Another report by CADTH highlights variation in the way gene therapies, including CAR T-cell therapies, are categorised by regulatory agencies, and inconsistent approaches have been noted.[24, 39] Canada has no formal definition for gene therapies, the EMA categorises gene therapy with other cell therapies under the category of Advanced Therapy Medicinal Products (ATMP), and the FDA categorises gene therapy as a regenerative medicinal therapy.[24] In the US, CAR T-cell therapies are assessed by the FDA's Center for Biologics Evaluation and Research (CBER) via the Office of Cellular, Tissue and Gene Therapies (OCTGT)[49], and in the EU they fall under the EMA's Committee for Advanced Therapies (CAT). Results of the searches highlighted various FDA–EMA initiatives to align regulatory processes (parallel scientific advice, an exchange fellowship program)[49], which could inform efforts to increase consistency with other agencies.

Frameworks for risk mitigation and safety monitoring

Regulatory summaries released by the FDA and EMA conclude that tisagenlecleucel and axicabtagene ciloleucel have favourable risk–benefit profiles if appropriate risk mitigation strategies are in place. The summaries outline plans for ongoing monitoring to mitigate the risk of observed safety issues in trials and assess potential long-term safety issues.[33, 53-55] The major risks of CAR T-cell therapies highlighted in the regulatory summaries include cytokine release syndrome (CRS) and neurologic toxicity (both of which can be life-threatening or fatal), infection, febrile neutropenia, and prolonged cytopenias. The FDA has implemented a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) and outlined the requirement for a 15-year post-marketing observational study to monitor long-term toxicities and the potential risk of secondary malignancies. The REMS outlined by the FDA for CAR T-cell therapy is based on procedures in the trials, including on-site training for participants, restricting study sites to transplant centres, and training and assessment of participating sites.

Further evidence for risk mitigation frameworks identified in the searches included an FDA presentation that detailed an office-wide review system and CAR T-cell working group to ensure a systematic approach to safety in light of the number of CAR T-cell and similar submissions entering the pipeline.[46] We noted that the FDA is developing prediction models to identify safety issues associated with CAR T-cell products and develop risk-mitigation strategies. Recommendations made within a 2018 consensus statement outline specific requirements for monitoring and managing adverse events arising from CAR T-cell therapy for paediatric B-ALL.[58] The EMA has also outlined plans for the post-authorisation monitoring of tisagenlecleucel and axicabtagene ciloleucel, including the certification of patient registries, which is discussed in the findings for research question 2.[16, 33]

Health technology assessment frameworks

Material collated from HTA body websites indicates challenges have arisen, or are anticipated, in the value assessment and delivery of CAR T-cell therapies. A report prepared by CADTH searched for HTA frameworks for evaluating gene therapies such as CAR T-cell therapy and did not identify any gene therapy guidelines or

frameworks produced by HTA bodies internationally.[24] CADTH conducted a survey of HTA agencies in Taiwan, Germany, Sweden and Australia and found variation in whether they considered CAR T-cell therapies would fall within their existing scope[24]; Taiwan has no plans for assessment because no therapies have been approved as yet, Germany and Sweden reported existing processes would be used, and an evaluation is underway in Australia on how best to approach the assessment of CAR T-cell therapy.

Britain's National Institute for Health and Care Excellence (NICE) has approved tisagenlecleucel for refractory paediatric B-ALL, and a decision about its use in adult DLBCL is pending. Axicabtagene ciloleucel has received an initial negative recommendation but the decision was under consultation at the time of writing and is yet to be finalised.[2-4] The NICE recommendation of tisagenlecleucel for B-ALL resulted in an agreement with Novartis for the therapy to be made available for eligible patients through the Cancer Drugs Fund (CDF). The CDF was set up to allow fast-track access to promising new treatments, via managed access arrangements, while further evidence was collected to address clinical uncertainty. In advance of the NICE HTAs, the University of York conducted a mock assessment[17] from which NICE concluded that its existing appraisal methods and decision framework were applicable to regenerative medicines and cell therapies.[18] CADTH is also assessing CAR T-cell therapies through its existing HTA process for medical devices and clinical interventions, in close collaboration with stakeholders.[25] The CADTH report and the mock NICE appraisal provide useful summaries of key challenges facing HTA bodies in the assessment of CAR T-cell therapies. These are:

- Gene therapies often do not fulfil the evidence and pricing requirements of current frameworks, guidelines and reimbursement models (e.g. size of the target population, burden of disease and unmet need)
- CAR T-cell therapies are mostly tested in single-arm studies with small populations due to the rareness of certain cancers and the ethical implications of withholding potentially life-saving treatment
- Value-based pricing models are limited by a lack of comparative or long-term efficacy data and uncertainty about pricing mechanisms and resources required for safe implementation
- Many trials are underway for multiple indications (see question 3), most including small numbers of patients
- Trial follow-up is often short and trials rely on response rather than survival, which causes difficulty for value-based assessment
- Comparators are poorly defined and vary across health systems.

Proposed solutions across key evidence sources include:[24, 17, 18, 25]

- Early and continued dialogue between manufacturers, regulators and payers to improve the quality of evidence and ensure criteria are being met, such as the EMA PRIME scheme
- Collection of real-world evidence by manufacturers which can be supported centrally by regulatory bodies for initial risk–benefit assessments and ongoing safety monitoring (see EMA Patient Registries Initiative and FDA database pilot summarised in research question 2)
- Horizon scanning by reimbursement and HTA bodies to develop awareness of emerging therapies and categorise different types for assessment
- Continued collaboration with patients, clinical experts and implementation groups to ensure priorities are captured and operational and implementation issues are addressed appropriately
- Quantifying clinical outcomes and decision uncertainty by HTA agencies for presentation to decision panels
- Development of innovative payment agreements to manage and share the risk of uncertainty while evidence is immature and allow patients access to medicines with potential substantial benefit. For example, negotiation of outcomes-based payments to offset the risk of high upfront

costs, as has been agreed between Novartis (manufacturer of tisagenlecleucel) and the US Centers for Medicare and Medicaid Services (CMS).[7]

Resources, funding mechanisms and access

It is acknowledged that specialist manufacturing resources, care centres and knowledge are required to deliver CAR T-cell therapy and manage novel toxicities, which should be reflected in associated costs.[20, 23, 37, 45] A comprehensive evidence review by the US-based Institute for Clinical and Economic Review (ICER) highlighted that both Novartis and Kite/Gilead have limited the availability of their CAR-T therapies to certified treatment centres, which has implications for access, although it is expected that the list of accredited centres will increase over time. US Medicare is convening an Evidence Development & Coverage Advisory Committee (MEDCAC), from which a decision memo for a national coverage analysis is due in February 2019.[26]

The extremely high cost of CAR-T therapies (US$350,000 to US$500,000 per patient before considering mark-up, costs of additional care and toxicity management) reflects their intensive manufacturing requirements, which has obvious implications for health system budgets and access. Evidence for funding arrangements identified in the search includes a recent announcement from US Medicare that reimbursement for tisagenlecleucel and axicabtagene ciloleucel was settled at a fee roughly equal to wholesale acquisition cost plus 6%.[36] However, doctors have expressed concerns that rules imposed by the companies regarding outpatient administration and subsequent hospital admission will result in failed reimbursement in some cases. In addition, Novartis has entered into an outcomes-based pricing arrangement with the Centers for Medicare and Medicaid Services (CMS) whereby payment will only be made for patients who have responded to tisagenlecleucel at the end of the first month.[7] Scenario analyses conducted by ICER indicate that the cost-effectiveness of CAR T-cell therapy is highly sensitive to hospital mark-ups and pricing arrangements agreed between the health provider and manufacturer.

Research Question 2: Where CAR T-cell therapies have been approved and are delivered within a regulatory framework, what is the evidence for the safety, efficacy and cost of these therapies?

Long-term and real-world data for the safety, efficacy and cost-effectiveness of CAR T-cell therapy are not yet available due to the length of time treatments have been available outside of clinical trials. Syntheses of clinical trial data provide useful overviews but are currently limited to the B-cell haematological malignancies for which CAR T-cell therapies have been approved (ALL, CLL and non-Hodgkin's lymphomas, primarily DLBCL). Comprehensive post-authorisation monitoring plans have been put in place by the EMA and FDA but are in their infancy.

Conclusions are currently limited by the size, non-comparative design and short follow-up of trials, and variations between them. As a result, there is currently no long-term evidence for important clinical outcomes such as overall survival (OS) and delayed onset toxicities, and results are subject to selection biases.[7, 11, 59] Single-arm trials prevent direct or indirect comparisons, and mean estimates comparing CAR T-cell therapy with alternative treatments are limited to naive or matched-population comparisons with historical control data. The evidence is therefore considered Grade III–3.[1]

Systematic reviews and economic analyses

The searches identified nine evidence syntheses that provide an overview of the safety, efficacy and cost-effectiveness of CAR T-cell therapy from completed clinical trials[5, 6, 8-13]; characteristics and summary results are provided in Appendix 6. The reviews vary in their approaches and inclusion criteria but overlap in their included studies. Reviews do not limit trial inclusion by geography, and only those conducting cost-effectiveness analyses are specific to a regulatory framework (FDA and EMA).

Analyses have mostly focused on tisagenlecleucel and axicabtagene ciloleucel (both autologous CAR T-cell therapies) using the pivotal studies (ELIANA, JULIET, ZUMA-1) and other early phase clinical trials. Three

cost-effectiveness analyses have assessed tisagenlecleucel compared with clofarabine and other comparators for paediatric ALL; one cost-effectiveness analysis by ICER also looks at the cost-effectiveness of axicabtagene ciloleucel versus salvage chemotherapy, and safety and efficacy results for tisagenlecleucel, for adult refractory DLBCL.[5, 7, 10] Additionally, four systematic reviews provide non-comparative efficacy and safety estimates of CD19-targeted CAR T-cell therapy for various B-cell malignancies by meta-analysing single-arm trials (between 5 and 17)[9, 11-13], and two further systematic reviews focus on adverse events (cytokine release syndrome [CRS][8] and tumour lysis syndrome [TLS]).[6]

All the evidence syntheses reviewed indicate substantial efficacy benefits of CAR T-cell therapy for B-cell malignancies compared with currently available alternatives, although the size of benefit varies. Pooled response estimates for systematic reviews covering multiple indications give an average response rate of about 60%, with favourable but variable results when indications are considered separately.[9, 12] CAR T-cell therapy appears to be most effective for ALL (75–93% response), followed by CLL (54–62% response) and NHL (36–39% response). Complete remission (CR) across conditions was achieved in between 15% and 20% of patients. Progression-free survival (PFS) varied, but approximately 43–50% were progression-free at six months, and 18–27% were progression-free at one year.[11, 13]

Focusing on paediatric B-ALL, the ICER report includes three single-arm trials of tisagenlecleucel (B2101J, B2205J and 2202/ELIANA; total N = 149) and makes naive indirect comparisons for efficacy outcomes with four trials of other FDA-approved therapies (clofarabine and blinatumomab). Overall remission ranged from 57–73% for tisagenlecleucel based on the full population (69–95% 'per-protocol' when only those infused were included) and from 20–63% for clofarabine and blinatumomab. The difference between the full 'intention-to-treat' population and 'per-protocol' results means real-world effectiveness is likely to be overestimated by systematic reviews based only on those who received treatment. Event-free survival (EFS) ranged from 46–60% at six months and 62–81% at 12 months for CAR T-cell therapy and from 11–35% and 20–38% at six and 12 months, respectively, for the comparators. It is noted that EFS at four years is a preferred clinical outcome, but long-term follow-up is not yet available. The base-case ICER for tisagenlecleucel versus comparators was US$45,871/quality-adjusted life-year (QALY) gained. Key drivers affecting cost-effectiveness in the economic model are listed in Appendix 6. Two additional cost-effectiveness analyses, one with a US focus[5] and one focused on British clinical practice[10], also report meaningful improvements in life expectancy and QALY gains compared with other treatments. The ICER review also contrasts its cost-effectiveness analysis with a mock analysis conducted by NICE prior to CAR T-cell therapy prices being available.[7, 17] The mock assessment for NICE highlighted that results were sensitive to the intent of CAR T-cell therapy (as a bridge to stem cell transplantation or as an intended cure), and the assumed cost and pricing structure of treatment (tested in scenario analyses by ICER).[17]

For the adult refractory lymphoma population (primarily DLBCL), the ICER report includes results from four studies: two testing axicabtagene ciloleucel (NCT00924326 and ZUMA-1/NCT02348216; total N = 123) and two testing tisagenlecleucel (NCT02030834 and JULIET/NCT02445248; total N = 127]). Efficacy results for the CAR T-cell therapies are compared by naive indirect comparison with those of historical controls from a large study of mixed salvage chemotherapies (SCHOLAR-1, N = 636). Overall response rate (ORR) was substantially higher for the CAR T-cell therapies than observed in the recent chemotherapy study: 82% and 73% in the axicabtagene ciloleucel studies, 64% and 53% in the tisagenlecleucel studies, and 26% for salvage chemotherapies. CR of adult refractory lymphoma was also substantially higher with both CAR T-cell therapies than in SCHOLAR-1: 73% and 55% for axicabtagene ciloleucel, 57% and 40% for tisagenlecleucel, and 7% for salvage chemotherapies. Promising results for EFS and OS were also noted in the ICER report, particularly in the earlier Phase I trials with longer follow-up. A cost-effectiveness analysis was conducted for axicabtagene ciloleucel, from which a base-case ICER versus salvage chemotherapy was derived as US$136,078/QALY gained. However, results were sensitive to several factors, which are listed in Appendix 6. In addition, the report cites a propensity-score-matched analysis of ZUMA-1 and SCHOLAR-1 conducted by

Neelapu and colleagues.[60] Propensity score matching is a method of adjusting for population differences between studies to reduce selection biases; while it is considered less prone to bias than naive indirect comparison, the assessment still carries biases that are normally controlled by randomisation. Adjusted results for axicabtagene ciloleucel versus salvage chemotherapies were 83% vs. 33% for ORR, 57% vs. 12% for CR, and 47% vs. 23% for estimated OS at 18 months. An estimated hazard ratio for OS was also calculated based on extrapolation, suggesting a large survival benefit of CAR T-cell therapy compared with current treatment of 0.28 (95% confidence interval 0.15 to 0.40).[60]

Severe adverse events that are commonly highlighted in trials and systematic reviews in 10% to 30% of patients across disease indications and types of CAR T-cell therapy are: CRS, neurotoxicity, fever, encephalopathy, kidney injury, hypotension, hypoxia, headache, infections, dyspnoea, neutropenia and B-cell aplasia. Severe CRS has affected more than half of patients treated with CAR T-cell therapy in some trials, and a meta-analysis reports pooled rates (with 95% CI) of 29.3% for B-ALL (12.3–49.1%), 38.8% for B-CLL (12.9–67.6%) and 19.8% for B-cell non-Hodgkin's lymphoma (B-NHL; 4.2–40.8%). Meta-regression identified differences between the malignancies in the effect of dose and tumour burden on risk of CRS[8] (Appendix 6). Another systematic review reports pooled rates of B-cell aplasia of 43.4% (15.1–76.8%). Overall, the wide confidence intervals around the pooled estimates reflect variability in observed rates and the uncertainty associated with small sample sizes. Rates of adverse events (all grades) and severe adverse events (Grade 3 or above requiring at least inpatient hospital care) observed in the pivotal trials were reported in the ICER report and have been reproduced in Appendix 6. The ICER review concludes that, while important harms occur commonly with both CAR T-cell therapies, they are manageable and perceived by clinicians as no worse than the serious adverse events associated with alternative treatments.

Overall, systematic reviews indicate substantial health benefits for the B-cell haematological malignancies studied compared with current treatment options. However, adverse events are common and can be life-threatening, the risk of delayed onset toxicity remains unknown, and there is substantial uncertainty in estimates of comparative effectiveness due to the size and single-arm design of early stage trials.

Post-authorisation monitoring plans

We found evidence for post-authorisation systems and risk mitigation strategies relating to the EMA and FDA regulatory approvals (see Appendix 6), considering the substantial safety concerns noted in clinical trials. Key safety issues highlighted by the EMA and FDA in the approval of tisagenlecleucel and axicabtagene ciloleucel are described above and for research question 1 under '*Frameworks for risk mitigation and safety monitoring*'. No results were identified from the post-authorisation monitoring studies and initiatives; plans for each are outlined below.

The FDA required Novartis to set up a long-term observational study for tisagenlecleucel (B2401) when it was approved for ALL, which was extended when the therapy was approved for DLBCL, to ensure the benefits of the therapy outweigh potential long-term safety issues. The study will include 15 years of follow-up to document adverse events and monitor potential development of secondary malignancies in the long term. B2401 plans to enrol 1000 patients with ALL over five years and at least 1500 patients with DLBCL.[53, 55] The FDA has outlined a similar post-marketing requirement from Kite Pharma to conduct a multicentre, prospective, observational safety study for axicabtagene ciloleucel using a registry design. As with tisagenlecleucel, the study will include 1500 subjects who will be followed for 15 years after their CAR T-cell infusion.[54]

Equivalent post-authorisation monitoring plans have been outlined by the EMA for axicabtagene ciloleucel and tisagenlecleucel in line with guidelines for safety and efficacy follow-up.[15, 33] Non-interventional post-authorisation safety and efficacy studies are planned for both therapies with regular follow-up until 2038. The EMA also requires periodic safety update reports and is investigating the potential use of existing patient registries to monitor safety. A report was identified from an EMA-hosted stakeholder workshop in

February 2018 that concluded registry data would play an essential role in risk–benefit evaluations and especially in post-authorisation data generation for CAR T-cell therapies.[16] The aim of the initiative is to engage with and certify key registries in the EU (European Society for Blood and Marrow Transplantation) and the US (Center for International Blood and Marrow Transplant Research) and make aggregate data available to stakeholders including regulators, authorisation holders and HTA agencies.[16] The report outlines plans to incorporate quality standards, electronic medical records, auditing and periodic reporting. The report highlights that the registry work is in line with ongoing plans by the European Network for Health Technology Assessment to bring together multiple groups to focus on the collection and sharing of core datasets through registries for HTA.[14]

In addition to the studies outlined above, the FDA has outlined Approved Risk Evaluation and Mitigation Strategies (REMS) for the approved CAR T-cell therapies, and is piloting a clinical safety database to inform regulatory review of CAR T-cell therapies. The database combines small studies that alone make risk–benefit analysis difficult, creates a platform to collate complex and variable data formats, facilitates electronic submission of safety information, and allows the FDA to provide advice to sponsors in the regulatory process about the safety concerns regarding a product class.[46] Since it is held centrally by the FDA there are no data-sharing limitations, and analyses can be standardised and performed automatically.

Research Question 3: What clinical trials have been conducted or are underway for CAR T-cell therapy?

Searches of clinical trials registries, company websites and non-commercial organisations found 390 clinical documented trials of CAR T-cell therapy for a range of cancers. The list of all trials identified — including trial identifiers, phase and recruitment status, population details, interventions and outcomes measured — is available in a supplementary Excel file. Only two trials of CAR T-cell therapy were identified for non-cancer indications: one in a population with HIV/AIDS (NCT03240328) and another for patients with systemic lupus erythematosus (NCT03030976). It is acknowledged that many CAR T-cell therapy trials are being conducted by non-commercial teams that may not all be documented on a clinical trial platform, meaning the number and nature of the trials landscape is difficult to capture accurately. We linked published abstracts and papers to the identified trials where possible, but 212 records that were deemed relevant could not be linked to a trial identifier.

Within the cancer trials identified from registries, only 21 are listed as available or completed and a further 42 are listed as active and not recruiting, all of which are Phase I (n =31) or Phase II studies (n = 11) with a single-arm design. Only two records have posted results on clinicaltrials.gov, but 58 have linked peer-reviewed abstracts or papers reporting results. No trials are listed as randomised and, where masking was described, all were open-label. Most studies are listed as recruiting or enrolling by invitation, highlighting the early stages of most research in the field (n = 267). Of the remaining studies, 28 are not yet recruiting, five are authorised, 10 have been terminated or withdrawn and four have unknown status.

Summaries and comparisons of the results of completed trials are difficult to make due to the rapidly growing and evolving evidence base, which covers a huge variety of populations, tumour targets, doses, manufacturing methods and outcome measures. Furthermore, the single-arm nature of the trials limits the conclusions that can be drawn about the efficacy, safety and cost-effectiveness of CAR T-cell therapy compared with alternative treatments. Results of recent systematic reviews, which are limited to populations with B-cell malignancy[5, 6, 8-13], are summarised under research question 2 and in Appendix 6.

The evidence searches identified numerous narrative syntheses of the clinical trial landscape with variable coverage, but three provided comprehensive overviews of CAR T-cell therapy research[59, 61, 62] (see Appendix 7). Key observations of clinical trials based on searches conducted for this Evidence Check, supplemented by the trial landscape papers, are as follows:

- Single and mixed population trials of B-cell and haematological malignancies, some recruiting larger populations, currently dominate the trial landscape[59]; 140 include at least one type of leukaemia (including ALL, CLL and acute myeloid leukaemia), 140 include lymphoma (including Hodgkin's and non-Hodgkin's lymphomas, primarily DLBCL), and 36 include multiple myeloma; 133 trials were documented at the end of 2016[61] and more than 200 were found in 2018
- Trials are mostly small and have a single-arm design[59, 61, 62]; 275/390 have a target population size of less than 50 and only 34 have a target population size of 100 or more
- Of those reporting age, most recruited only adults (mostly 18+ or 18–75 years), 63 are recruiting a range of ages (children and adults) and 31 are recruiting children and young adults
- Trials are in progress for a range of solid tumour types including, but not limited to, renal cell carcinoma, pancreatic and pleural adenocarcinoma, glioblastoma, neuroblastoma, and gastric, thyroid, ovarian and breast cancers; it is acknowledged that the application of CAR T-cell therapy to solid tumours poses various challenges, and trials with results are showing less favourable outcomes than have been seen in the B-cell haematological cancers[59, 61]
- Most trials are being conducted in the US (74/~100 in 2016) but many are underway around the world, including in China, Europe, Japan and Australia
- In Australia, recruitment is underway or starting soon for international trials in adult and paediatric aggressive lymphoma, low-grade lymphoma and relapsed ALL (all with off-site manufacturing). An Australian early stage Phase I trial with local manufacturing is also underway in solid cancers, and a trial for myeloma is in the preclinical phase
- CD19 is the most common target but numerous others are being studied (notably CD20, CD22, Igk and B-cell maturation protein BCMA)[59, 62]; identifying successful target antigens for non-B-cell malignancies and solid tumours has proved challenging
- Most completed studies have used an autologous cell source (i.e. from the patient)[62]
- Phase I trials are exploring strategies to reduce on-target/off-tumour autoreactivity of CAR T-cells towards healthy tissue, such as 'suicide genes' and safe dosing strategies[59] but Phase I results are emerging for allogeneic CAR T-cell therapies (e.g. UCART19)
- Safety outcomes are listed consistently, but variation is noted across disease areas and methodologies for efficacy outcomes[62]; commonly listed outcomes are rates of complete remission and overall response.

Gaps in the evidence

- Evidence for regulatory frameworks and HTA are limited to North America and Europe and may not be applicable to other health systems
- Post-authorisation studies are planned but are in the early stages and most have not yet reported results
- Clinical trials of CAR T-cell therapies are currently limited to single-arm, open label, Phase I and II studies with short follow-up, which poses challenges for the assessment of treatment durability and long-term safety.

Discussion

We conducted comprehensive and systematic searches to identify international evidence about the status of CAR T-cell regulation, and efforts to assess safety and efficacy before and after authorisation. Relevant resources included peer-reviewed studies and systematic reviews, regulatory and governmental reports and presentations, HTAs and research bulletins. While this Evidence Check sought a wide range of evidence from grey literature resources, it is acknowledged that further information is likely to be held by regulators and manufacturers that is not freely available. We extracted and synthesised evidence to provide an overview of the challenges faced by regulatory bodies and HTA agencies, and proposed approaches to ensure patients with life-threatening cancers have safe access to promising treatments.

Existing regulatory frameworks for advanced and regenerative medicines have been applied successfully to two autologous CAR T-therapies, tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) in the European Union and US. Further CAR T-cell therapies are in the EMA and FDA pipelines, and progress is being made to assess and implement CAR T-cell therapies in Australia, China, Japan and Canada. The experiences of the FDA and EMA, together with evidence from inter-agency initiatives, suggest the regulation of CAR T-cell therapies internationally will benefit from collaboration in the generation of centralised datasets and repositories to support risk–benefit analysis. Specialist designations (e.g. PRIME, Breakthrough Therapies, scientific advice etc.) have been employed to allow flexibility in the level of evidence required and to enable regulators to support and shape evidence generation. Unique and complex safety issues have required regulators to devise post-authorisation safety plans to allow patients early access to promising medicines while building longer-term datasets. The possibility of outcomes-based payment systems may mitigate the risk of uncertainty until longer-term data have been generated.

Evidence syntheses to provide overviews of the efficacy, safety and cost-effectiveness of CAR T-cell therapies are currently limited by the size and single-arm design of early stage trials, and variation between them. Overall, systematic reviews indicate substantial health benefits of autologous CAR T-cell therapies (primarily tisagenlecleucel and axicabtagene ciloleucel), with overall response ranging from 36–93% in systematic reviews of different B-cell haematological malignancies; results appear most promising for paediatric B-ALL, while early results in other cancers are less favourable, particularly solid tumours. Results based on full intention-to-treat populations are less favourable than those based only on patients who received treatment, and the latter may overestimate real-world effectiveness. Limited follow-up means the durability of treatment effects is unknown, which has implications for the assessment of cost-effectiveness. Adverse events are common and can be life-threatening, the risk of delayed onset toxicity remains unknown, and there is substantial uncertainty in estimates of comparative effectiveness. Research is focusing on strategies to reduce and manage toxicity and, while risk mitigation strategies mandated by the FDA and EMA are in their infancy, coordinated initiatives aim to capture long-term data as CAR T-cell therapies are implemented.

Challenges are also faced by bodies involved in the implementation of CAR T-cell therapies. CAR T-cell therapies require specialist infrastructure and training, and there has been difficulty ensuring purity and potency due to individual manufacturing procedures. Implementation assessments should acknowledge the time and infrastructure required to manufacture and ship CAR T-cell therapies, and training of specialist staff to manage novel toxicities. There is a precedent for outcomes-based payment in the US, which may enter discussions for future approvals to mitigate uncertainty until more mature robust data are available.

Implications for Australia

Australia is likely to encounter similar issues in the assessment of CAR T-cell therapies as the countries and regions where these types of therapies have already been assessed and approved; these include the complex and potentially long-term safety issues related to the persistence of the treatment's biological activity in the immune system combined with an evidence base limited to single-arm trials with short follow-up and small patient populations. Another issue has been the legislation that should apply to CAR T-cell therapy, which needs to be determined in Australia. Australia would also benefit from assessing whether existing regulatory and HTA processes can be used to assess CAR T-cell therapies. Several issues specifically affect the value assessment of CAR T-cell therapies:

- The long-term risks of these therapies are largely unknown but potentially substantial, which leads to challenges and uncertainty for value assessment
- The specialist manufacturing resources, care centres and knowledge required to deliver CAR T-cell therapy and manage novel toxicities should be reflected in associated costs
- There is a need to develop innovative payment agreements to manage and share the risk of uncertainty while evidence is immature and to allow patients access to medicines with potential substantial benefit, e.g. negotiating outcomes-based payments to offset the risk of high upfront costs
- The lack of familiarity with regulatory processes among those developing the treatments (more often universities or non-commercial bodies rather than pharmaceutical companies) that has been seen in other countries is likely to continue, and to be the case also for Australia, as indicated by the large number of ongoing studies and associated organisations identified in this review.

As mentioned previously in this report, there are several factors affecting access to and resources for delivery of CAR T-cell therapies which will need to be considered in a local and national context, such as the number, location and accreditation of facilities; and the expertise needed to deliver CAR T-cell therapy safely and manage toxicities.

Number, location and accreditation of facilities

- The two companies with currently approved CAR T-cell therapies, Novartis and Kite/Gilead, have limited the availability of their therapies to certified treatment centres, which has implications for access
- Australia currently has no accredited sites, but existing sites that are good manufacturing process (GMP) compliant could be accredited to manufacture CAR T-cells
- The length of time taken to manufacture the therapies (weeks or months), and the need to implement cell shipping and tracking systems to ensure safety
- Difficulty ensuring purity and potency due to individual manufacturing procedures

Expertise needed to deliver CAR T-cell therapy safely and manage toxicities

It is recommended that Australia develop and implement its own strategy for risk evaluation and mitigation. This could include:

- Restriction of therapy to qualified centres, e.g. transplant centres
- Training and assessment of participating centres
- Careful long-term follow-up assessment of patients
- Leverage existing intensive care and bone marrow transplant registries
- Specially adapted services for paediatric patients.

Conclusion

The speed with which the research into CAR T-cell therapy and other gene therapies has progressed is reflected in the proliferation of peer-reviewed research, guidelines and regulatory documents retrieved by this Evidence Check. Countries where CAR T-cell therapy has yet to be approved can learn from the experiences of agencies that have adapted processes and found initiatives to cope with the challenges posed by the wide range of CAR T-cell therapies coming through the pipeline.

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Appendices

APPENDIX 1: Electronic database searches

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (searched 26/06/2018)		
1	Receptors, Antigen, T-Cell/	21559
2	(chimeric OR artificial OR modified OR engineered).tw.	655739
3	1 and 2	1788
4	((CAR or CARs or CAR-modified or chimeric antigen receptor$) adj3 (T cell or T-cell or T cells or T-cells or T lymphocyte$ or T-lymphocyte$)).tw.	1843
5	(cart-19 or ucart$).tw.	9
6	((CART or CAR-T or CAR T or chimeric antigen receptor$) adj3 (therap$ or treat$ or immunity or immunotherap$ or cell)).tw.	3256
7	((chimeric OR artificial OR modified OR engineered) adj3 (T cell or T-cell or T cells or T-cells or T lymphocyte$ or T-lymphocyte$ or immunoreceptor$)).tw.	2742
8	(axicabtagene ciloleucel or Axi-Cel or Yescarta).tw.	1123
9	Zuma-1.tw.	5
10	(tisagenlecleucel or Kymriah or CTL019).tw.	42
11	(KTEC19 or KTE-C19).tw.	7
12	(Lisocabtagene maraleucel or JCAR$).tw.	29
13	or/3-12	6352
14	exp neoplasm/	3052491
15	13 and 14	1846
16	limit 15 to (case reports or editorial or historical article or letter)	99
17	15 not 16	1747
18	(animals not humans).sh	4433879
19	17 not 18	1643
20	limit 19 to yr="2015 -Current"	826

Embase 1974 to 2018 June 25 (searched 25/06/2018)		
1	exp T lymphocyte receptor/	41640
2	(chimeric OR artificial OR modified OR engineered).tw.	796162
3	1 and 2	3040
4	((CAR or CARs or CAR-modified or chimeric antigen receptor$) adj3 (T cell or T-cell or T cells or T-cells or T lymphocyte$ or T-lymphocyte$)).tw.	3775
5	(cart-19 or ucart$).tw.	69
6	((CART or CAR-T or CAR T or chimeric antigen receptor$) adj3 (therap$ or treat$ or immunity or immunotherap$ or cell)).tw.	5621
7	((chimeric OR artificial OR modified OR engineered) adj3 (T cell or T-cell or T cells or T-cells or T lymphocyte$ or T-lymphocyte$ or immunoreceptor$)).tw.	4891

8	(axicabtagene ciloleucel or Axi-Cel or Yescarta).tw.	40
9	Zuma-1.tw.	40
10	(tisagenlecleucel or Kymriah or CTL019).tw.	161
11	(KTEC19 or KTE-C19).tw.	51
12	(Lisocabtagene maraleucel or JCAR$).tw.	112
13	or/3-12	11335
14	exp neoplasm/	4111471
15	13 and 14	5010
16	limit 15 to (case reports or editorial or historical article or letter)	70
17	15 not 16	4940
18	Animals/ not Humans/	1350109
19	17 not 18	4921
20	limit 19 to yr="2015 -Current"	2901

Cochrane Library (Cochrane Central Register of Controlled Trials [CENTRAL], Database of Abstracts of Reviews of Effects [DARE]. NHS Economic Evaluation Database [NHS EED], (searched from inception to 26 June 2018).		
1	MeSH descriptor: [Receptors, Antigen, T-Cell] explode all trees	103
2	chimeric OR artificial OR modified OR engineered	50641
3	#1 and #2	6
4	(CAR or CARs or CAR-modified or "chimeric antigen receptor*") near/3 ("T cell" or T-cell or "T cells" or T-cells or "T lymphocyte*" or T-lymphocyte*)	141
5	cart-19 or ucart*	2
6	(CART or CAR-T or "CAR T" or "chimeric antigen receptor*") near/3 (therap* or treat* or immunity or immunotherap* or cell)	331
7	(chimeric OR artificial OR modified OR engineered) near/3 ("T cell" or T-cell or "T cells" or T-cells or "T lymphocyte*" or T-lymphocyte* or immunoreceptor*)	115
8	"Lisocabtagene maraleucel" or JCAR*	50
9	"axicabtagene ciloleucel" or Axi-Cel or Yescarta	13
10	Zuma-1	17
11	tisagenlecleucel or Kymriah or CTL019	17
12	KTEC19 OR KTE-C19	23
13	#3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	441
14	MeSH descriptor: [Neoplasms] explode all trees	78275
15	#13 and #14	24

APPENDIX 2: Clinical trial registry searches

Clinicaltrials.gov (searched 19/06/2018) — Limited to last updated after 01 Jan 2015		
Intervention	chimeric antigen receptor OR car-t OR car t-cell OR car t cell OR Lisocabtagene maraleucel OR JCAR017 OR JCAR015 OR KTE-C19 OR tisagenlecleucel OR Kymriah OR CTL019 OR Zuma-1 OR axicabtagene ciloleucel OR Yescarta OR ucart OR cart-19	460
Condition	Cancer	364

WHO ICTRP (searched 06/07/2018) In advanced search, recruitment status ALL, not limited by date or phase		
Intervention	chimeric antigen receptor OR car-t OR car t-cell OR car t cell OR Lisocabtagene maraleucel OR JCAR017 OR JCAR015 OR KTE-C19 OR tisagenlecleucel OR Kymriah OR CTL019 OR Zuma-1 OR axicabtagene ciloleucel OR Yescarta OR ucart OR cart-19	68
Condition	Cancer	

APPENDIX 3: Grey literature searches

OpenGrey.eu (searched 06/07/2018) Limited to English language	
chimeric antigen receptor OR car-t OR car t-cell OR car t cell OR Lisocabtagene maraleucel OR JCAR017 OR JCAR015 OR KTE-C19 OR tisagenlecleucel OR Kymriah OR CTL019 OR Zuma-1 OR axicabtagene ciloleucel OR Yescarta OR ucart OR cart-19	44
chimeric AND cancer	12
chimeric AND t cell	17
chimeric AND t-cell	9
cell therapy AND t cell AND chimeric	5
cell therapy AND cancer AND t cell	30
regenerative AND cancer	6
regenerative AND t cell	4
regenerative AND t-cell	1
chimeric immune receptor	6
cell immunotherapy AND t cell	41
cell immunotherapy AND t-cell	33
cell immune therapy AND t cell	44
cell immune therapy AND t-cell	34
cell immunotherapy AND cancer	35
cell immune therapy AND cancer	24
gene therapy AND t cell	30
gene therapy AND t-cell	15
CAR AND therapy	15
CAR AND cancer	34
cellular therapy AND cancer	58

cellular therapy AND t cell	28
cellular therapy AND t-cell	18

HTA bodies (between 20 and 27 June)	
European Union	European Medicines Agency
Britain	NICE, Healthcare improvement Scotland, SIGN, HTW — Health Technology Wales, NIHR — National Institute for Health Research
US	Medicare Coverage Advisory Committee, ICER, Agency for Healthcare Research and Quality (AHRQ), Center for Medical Technology Policy (CMTP), ECRI Institute, Medical Technology and Practice Patterns Institute (MTPPI), The National Working Group on Evidence-Based Health Care, CENTER FOR DRUG EVALUATION AND RESEARCH (CDER/FDA)
China	Peking University Centre for Evidence-Based Medicine and Clinical Research, Chinese food and drug administration
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH), Committee to Evaluate Drugs (CED), Health Policy, Management, and Evaluation, Health Quality Ontario, Institute for public health Calgary university, INESSS – Institut national d'excellence en santé et en services sociaux, Institute of Health Economics, Programs for Assessment of Technology in Health (PATH) Research Institute, THETA (Toronto Health Economics and Technology Assessment Collaborative)
Japan	Department of Technology Assessment and Biostatistics, Ministry of Health, Labour and Welfare (regulatory body)
Armenia	Ministry of Health, Scientific Centre of Drug and Medical Technology Expertise
Austria	Institute of Technology Assessment, The Ludwig Boltzmann Institut [for] Health Technology Assessment (LBI for HTA), Bundesministerium für Gesundheit (Federal Ministry of Health)
Belarus	Ministry of Health, The Republican Scientific and Practical Center of Medical Technologies, Informatization, Management and Economics of Public Health
Belgium	Belgian Health Care Knowledge Centre, Federal Public Service Health, Food Chain Safety and Environment, Center for Health Services and Nursing Research (University of Leuven), Health Research for Action
Bosnia-Herzegovina	Ministry of Health, Agency for Medicines and Medical Devices of Bosnia and Herzegovina
Bulgaria	Bulgarian Drug Agency (Ministry of Health), The National Council on Drug Pricing and Reimbursement (NPRC)
Croatia	Ministry of Health, Agency for Medicinal Products and Medical Devices
Cyprus	Ministry of Health
Czech Republic	State Institute for Drug Control
Denmark	Ministry of Health, Danish Centre for Evaluation and HTA (DACEHTA), Danish Institute for Health Services Research and Development (DSI) – now merged as KORA
Estonia	Ministry of Health
Finland	National HTA Coordination Unit (FinCCHTA, formerly The Finnish Office for Health Care Technology Assessment)
France	L'Agence nationale de sécurité du médicament et des produits de santé (ANSM), La Haute Autorité de santé (HAS), CEDIT — Comité d´Evaluation et de Diffusion des Innovations Technologiques
Georgia	Ministry of Labor, Health and Social Protection

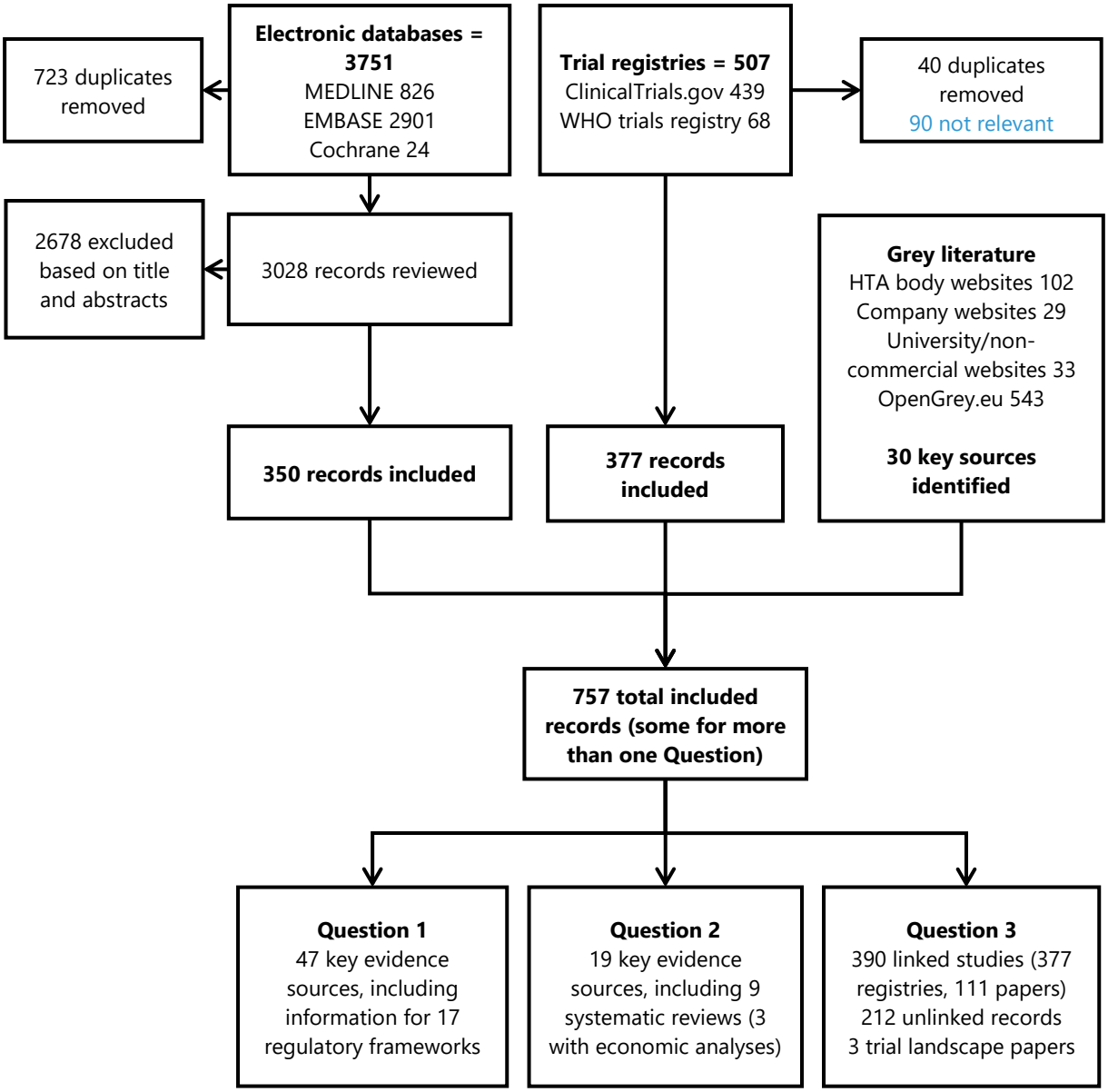
Germany	German Agency for HTA at the German Institute for Medical Documentation and Information, Institut für Qualität und Wirschaftlichkeit im Gesundheitswesen (IQWIG), Federal Joint Committee, Office of Technology Assesment of the German Parliament-MHH Hannover Medical School,
Greece	Ministry of Health, National Organization for Medicines
Hungary	Ministry of Human Resources
Ireland	HIQUA — Health Information and Quality Authority, Medicines Board
Italy	The Italian Medicines Agency, Agenas — The National Agency for Regional Health Services, ASSR — Agenzia Sanitaria e Sociale Regionale (Regional Agency for Health and Social Care), UVT – HTA Unit in A. Gemelli Teaching Hospital
Latvia	State Agency of Medicines of Latvia
Lithuania	Ministry of Health, State Health Care Accreditation Agency, State Medicines Control Agency, Institute of Hygiene
Luxembourg	Ministry of Social Security
Netherlands	Health Council of the Netherlands
Norway	Norwegian Institute of Public Health
Poland	Ministry of Health, Agencja Oceny Technologii Medycznych, Agency for HTA in Poland, AHTAPol — Agency for Health Technology Assessment in Poland
Portugal	National Institute of Pharmacy and Medicines (INFARMED)
Slovakia	State Institute for Drug Control, Ministry of Health
Slovenia	National Institute of Public Health of the Republic of Slovenia, Health Insurance Institute of Slovenia HIIS
Spain	Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud Carlos III, Catalan Agency for Health Technology Assessment, OSTEBA — Basque Office for Health Technology Assessment, Spanish Agency of Medicines and Medical Devices, Andalusian Agency for Health Technology Assessment, AQuAS — Agència de Qualitat i Avaluació Sanitàries de Catalunya, AVALIA-T — Galician Agency for Health Technology Assessment, IACS — Health Sciences Institute in Aragon
Sweden	Swedish Medical Products Agency (MPA), SBU — Swedish Agency for Health Technology Assessment
Switzerland	Federal Office of Public Health, TA-SWISS
Turkey	Ministry of Health, Turkish Medicines and Medical Devices Agency
Terms searched in all sites	Chimeric antigen; CAR-T; CAR T; CAR; tisagenlecleucel; Kymriah; CTL019; axicabtagene ciloleucel; Yescarta; Axi-Cel; JCAR017; Lisocabtagene maraleucel; liso-cel
Additional terms added for US, Britain, France, Germany, Japan, Canada, Spain, Italy	Regenerative medicine; cell therapy; chimeric; JCAR, cell immune therapy; cell immunotherapy; gene therapy; cellular therapy

Academic institution and non-commercial organisations (9 to 20 July)

9 July	Cancer research UK, Fred Hutchinson Cancer Research Center
10 July	Worldwide Cancer Research, Macmillan, The Institute of Cancer Research, Cancer Research Wales, The Cancer Treatment and Research Trust, World Cancer Research Fund, Bone Cancer Research Trust, Bowel and Cancer Research, Prostate Cancer Research Centre, Alliance for Cancer Gene Therapy, NIH National Cancer Institute, Gateway for Cancer Research, Cancer Research Institute
19 July	University of Washington, Dana-Farber Cancer Institute, MD Anderson Cancer Center, University of Texas, Memorial Sloan Kettering Cancer Center, University of Pennsylvania, Moffitt Cancer Center, Stanford University, UCL Cancer Institute, University of Birmingham, University of Southampton
20 July	University of Manchester, University of Toronto, University of Chicago, Myeloma UK, University of Maryland, Vanderbilt University, Osaka University, University Hospital Würzburg
Terms searched in all sites	Chimeric antigen; CAR-T; CAR T; CAR; tisagenlecleucel; Kymriah; CTL019; axicabtagene ciloleucel; Yescarta; Axi-Cel; JCAR017; Lisocabtagene maraleucel; liso-cel; regenerative medicine; cell therapy; chimeric; JCAR, cell immune therapy; cell immunotherapy; gene therapy; cellular therapy

Manufacturer/company websites (13 to 18 June 2018)	
List derived from Who's doing CAR-T and CAR-T Companies: The Meteoric Rise of Cellular Immunotherapies	Novartis, Gilead (acquired Kite Pharma), Sorrento therapeutics, Cellectis (Servier/Pfizer collaboration), Celyad, Juno Therapeutics, Celgene, Mustang Bio, ZIOPHARM, Allogene Therapeutics, Amgen, Agios Pharmaceutical, Bellicum Pharmaceuticals, CARsgen Therapeutics, Cell Design Labs (acquired by Gilead/Kite Pharma), Celularity, Fate Therapeutics, Fortress Bio, Janssen Biotech, JW Therapeutics, Medisix Therapeutics, Nanjing Legend Biotech, Pfizer, Poseida Therapeutics, Servier, Shire, Precision BioSciences, Baxalta (acquired by Shire)
Terms searched in all sites	Chimeric antigen; CAR-T; CAR T; CAR; tisagenlecleucel; Kymriah; CTL019; axicabtagene ciloleucel; Yescarta; Axi-Cel; JCAR017; Lisocabtagene maraleucel; liso-cel; regenerative medicine; cell therapy; chimeric; JCAR, cell immune therapy; cell immunotherapy; gene therapy; cellular therapy

APPENDIX 4: PRISMA flow diagram detailing the evidence search and sift process



APPENDIX 5: Regulatory approvals and assessment frameworks identified for Research Question 1

Country	Body	Product	Status/dates	Condition/indication	Method of evaluation/details
US	FDA	Tisagenlecleucel (Novartis)	First approved Aug 2017	B-ALL, relapsed or refractory (up to 25 yrs)[53]	Assessed by the Center for Biologics Evaluation and Research (CBER) Office of Tissues and Advanced Therapies (OTAT)
		Tisagenlecleucel (Novartis)		DLBCL, no response to, or relapse after, 2+ other treatments (adults)	As above
US	FDA	Axicabtagene ciloleucel (Kite/Gilead)	Approved Oct 2017	DLBCL, no response to, or relapse after, 2+ other treatments (adults)	As for Tisagenlecleucel
US	FDA	Lisocabtagene maraleucel (JCAR017), Juno Therapeutics, Celgene	Unknown	DLBCL, relapsed or refractory	Phase I trial, progressing through the regulatory process as a breakthrough therapy[20]
US	FDA	Bb2121, Bluebird Bio, Celgene	Unknown	Multiple myeloma, relapsed or refractory	Phase I/II trial, progressing through the regulatory process under the breakthrough therapy conditions[20]
EU	EMA	Axicabtagene ciloleucel (Kite Pharma)	Recommended Jun 2018, full authorisation granted August 2018	DLBCL and PMBCL after 2+ lines of systemic therapy (adults) Nb. Orphan designations granted for CLL/SLL	Assessed by Committee for Advanced Therapies (CAT) as a gene therapy; application supported through the PRIority MEdicines scheme (PRIME, granted 2016). Orphan designation assessed 2014 and 2016
EU	EMA	Tisagenlecleucel (Novartis)	Recommended Jun 2018, full authorisation granted August 2018	B-ALL, refractory or in second line or later relapse (up to 25 years)	
EU	EMA	Tisagenlecleucel (Novartis)		DLBCL, after 2+ lines of systemic therapy (adults)	
EU	EMA	Axicabtagene ciloleucel (Kite Pharma)	In progress	ALL, CLL/SLL, FL	Orphan designations granted for axicabtagene ciloleucel, status of assessment unknown.

Country	Body	Product	Status/dates	Condition/indication	Method of evaluation/details
EU	EMA	Lisocabtagene maraleucel (JCAR017), Juno Therapeutics, Celgene	Unknown	DLBCL, relapsed or refractory	Phase I trial, progressing through regulatory process under the PRIME scheme[20]
EU	EMA	Bb2121, Bluebird Bio, Celgene	Unknown	Multiple myeloma, relapsed or refractory	Phase I/II trial, progressing through the regulatory process supported by the PRIME scheme[20]
England and Wales	NICE	Axicabtagene ciloleucel (Kite Pharma)	Initial negative decision, final decision pending	DLBCL, PMBCL and follicular lymphoma [ID1115]	All assessed through the standard technology appraisal system, not as a highly specialised technology Tisagenlecleucel will be funded through the Cancer Drugs Fund, a mechanism set up to provide fast-track access to promising new cancer treatments. Data will be collected about patients receiving the treatment through the fund to reduce uncertainty
England and Wales	NICE	Tisagenlecleucel (Novartis)	Expected late 2018	DLBCL, relapsed or refractory [ID1166]	
England and Wales	NICE	Tisagenlecleucel (Novartis)	Recommended through CDF August 2018	B-ALL, previously treated (3–25 years) [ID1167]	
England and Wales	NICE	CAR T-cell therapy	2016	B-ALL, relapsed or refractory (children and young adults)	Mock HTA to test the application of NICE appraisal methodology to regenerative medicines and cell therapies using a hypothetical dataset
Canada	Health Canada	Tisagenlecleucel (Novartis)	September 2018	B-ALL, relapsed or refractory (3–25 years) and adult relapsed or refractory B-cell lymphoma	Approved following a Priority Review
Canada	CADTH	CAR T-cell therapies	No expected date	Not specified	Health technology assessment process for medical devices and clinical interventions (not through its pan-Canadian Oncology Drug Review [pCODR] or Common Drug Review [CDR])

Abbreviations used in table: B-ALL, B-cell acute lymphoblastic leukaemia; CADTH, Canadian Agency for Drugs and Technologies in Health; CDF, Cancer Drugs Fund; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; EU, European Union; FL, follicular lymphoma; NICE, National Institute for Health and Care Excellence; PMBCL, primary mediastinal B-cell lymphoma; SLL, small lymphocytic lymphoma; US, United States of America.

Note: axicabtagene ciloleucel is otherwise known as Yescarta or KTE-C19; tisagenlecleucel is otherwise known as Kymriah or CTL019

APPENDIX 6: Safety, efficacy and cost of CAR T-cell therapy (Research Question 2)

Safety, efficacy and cost of CAR T-cell therapy — systematic reviews and economic analyses (Research Question 2)

Source/ID	Design	Condition/ indication	Comparison	N studies (patients)	Safety	Efficacy	Cost-effectiveness
Intitute for Clinical and Economic Review (ICER)[7]	Systematic review of RCTs, observational studies and single-arm trials Comparisons are naive based on historical controls; direct or indirect comparisons not possible US focus	B-ALL, relapsed or refractory (up to 25 years)	Tisagenlecleucel Clofarabine and blinatumomab	3 studies (N=149) 4 studies (N=196) for comparators	% with any grade AE (grade 3+ in brackets) in main Tis study (ELIANA, n=68): CRS 79% (49%) Neurotoxicity 65% (18%) Fever 50% (15%) Encephalopathy 34% (10%) Headache 37% (3%) Acute kidney injury 22% (13%) Hypotension 31% (22%) Hypoxia 24% (18%) Infection NOS 41% (16%) Viral infection 26% (18%) Bacterial infection 19% (13%) Fungal infections 13% (7%)	Naive comparisons of 3 Tis studies with 4 comparator studies: Overall remission in Tis studies ranges from 57–73% in ITT (69–95% for those infused) and from 20–63% for comparators EFS at 6m ranged from 46–60% for Tis vs. 11–35% for comparators, and from 62–81% and 20–38%, respectively, at 12 months	Base-case ICER US$45,871/QALY gained. Key drivers: duration of IVIG for B-cell aplasia, % discount for future clinical benefits, % hospital mark-up; ICER within acceptable thresholds across broad ranges of model inputs Various scenarios including alternative payment strategies
		Adult refractory B-cell lymphoma (primarily DLBCL)	Axi-cel Salvage chemotherapies	2 studies (N=123) 1 study (N=636) for comparator	% with any grade AE (grade 3+ in brackets) in main Axi study (ZUMA-1, n=101): CRS 94% (13%) Neurotoxicity 87% (31%) Fever 86 (16%) Encephalopathy 57% (29%) Headache 45% (1%)	Naive comparisons of 2 Axi studies with chemo study: ORR Axi 73% and 82% vs. chemo 26% CR: Axi 73% and 55% vs. chemo 7% Propensity-score-matched ZUMA-1 (Axi) and	Base-case ICER US$136,078/QALY gained Key drivers: % discount for future clinical benefits, utility for "alive/responding to treatment" health state, % hospital mark-up,

Source/ID	Design	Condition/ indication	Comparison	N studies (patients)	Safety	Efficacy	Cost-effectiveness
					Renal insufficiency 12% (5%) Hypotension 57% (15%) Hypoxia 32% (11%) Infections NOS 26% (16%) Viral infections 16% (4%) Bacterial infection 13% (9%) Fungal infection 5% (NR)	SCHOLAR-1 (chemo)[60] estimates: ORR Axi 83% vs. chemo 33% CR Axi 57% vs. chemo 12% OS HR of 0.28 (95% CI 0.15–0.40), and 18m OS axi 47% vs. chemo 23%	standardised mortality ratio, duration of IVIG for B-cell aplasia; ICER frequently above acceptable thresholds Various scenarios
			Tisagenlecleucel Salvage chemotherapies	2 studies (N=127) 1 study (N=636) for comparator	% with any grade AE (grade 3+ in brackets) in main Tis study (JULIET, n=99): CRS 58% (23%) Neurotoxicity 21% (12%) Infections 34% (20%) 28-day+ cytopenia 36% (27%) Febr. neutropenia 13% (13%) TLS 1% (1%)	Naive comparisons of 2 Tis studies with chemo study: ORR: Tis 53% and 64% vs. chemo 26% CR: Tis 40% and 57% vs. chemo 7%	Not assessed
Hao (2017)[5]	Cost-effectiveness analysis US focus	Relapsed or refractory paediatric/ young adult patients (pts) with B-ALL	Tisagenlecleucel Clofarabine, blinatumomab, salvage chemotherapies, allogeneic SCT	3 single-arm trials	Not reported	Not reported	Treatment with CTL019 led to an increase of from 2.31 (vs. allogeneic SCT) to 4.29 (vs. clofarabine) discounted QALYs and value-based prices (defined as the price that would achieve ICERs of US$100k, US$150k, US$200k and US$300k per QALY gained, for CTL019 vs. each comparator) ranged from US$488,470

Source/ID	Design	Condition/ indication	Comparison	N studies (patients)	Safety	Efficacy	Cost-effectiveness
							(vs. salvage chemotherapy, ICER US$100k) to US$1,364,525 (vs. clofarabine, ICER US$300k)
Howard (2016)[6]	Systematic review of TLS with novel therapies	Persistent B-cell cancer post allogeneic hematopoietic SCT	Single-agent CD19-targeted CAR T-cell therapy No comparator	7 published studies, 1 Phase II trial reported TLS	1/10 developed TLS 8 days after infusion, despite prophylactic allopurinol 1 day before infusion Rasburicase used to manage serum uric acid levels	Not assessed	Not assessed
Jin (2018)[8]	Systematic review of Phase I studies reporting severe CRS	B-cell CD19 cancers: B-ALL, B-CLL, B-NHL	CD19-targeted CAR T-cell therapy No comparator	19 studies (N=313)	Pooled rates of severe CRS (95% CI): B-ALL 29.3% (12.3–49.1%) B-CLL 38.8% (12.9–67.6%) B-NHL 19.8% (4.2–40.8%) Univariate meta-regression showed total infusion cell dose contributed to severe CRS in B-ALL but not in B-CLL or B-NHL. Tumour burden strongly associated with CRS severity in B-ALL only	Not assessed	Not assessed
Riaz (2017)[9]	Systematic review and meta-analysis of Phase I and II trials	B-cell haematologic cancers: B-ALL, B-CLL and NHL	CD-19 and CD-20 chimeric antigen receptor-T therapy	16 studies (N=195); various with mixed populations	Pooled rates of major adverse events (95% CI) in single-arm trials: CRS 34.6% (26.4–43.8%)	Pooled analysis of single-arm trials: ORR 61%; CR 42% Event rate (%) by cancer (95% CI):	Not assessed

Source/ID	Design	Condition/ indication	Comparison	N studies (patients)	Safety	Efficacy	Cost-effectiveness
			No comparator		Severe neurotoxicity 35.1% (27.1–44.1%) B-cell aplasia 43.4% (15.1–76.8%)	B-ALL ORR 74.6% (55.4–87.5%) CR 71.3% (40.9–89.9%) B-CLL: OR 54.3% (35.3–72.1%) CR 32.5% (19.4–49.1%) Non-Hodgkin's: OR 51.0% (38.7–63.1%) CR 24.9% (16.0–36.5%)	
Snider (2017)[10]	Economic analysis expanding on the NICE mock HTA British focus	Patients under age 30 with relapsed or refractory B-ALL	Tisagenlecleucel vs. clofarabine	10 studies (N=380)	Not reported	Not reported	Patients gained an average of 10.1 QALYs per patient from CTL019 treatment relative to clofarabine About 1/3 of total value of the QALY gain was attributable to added patient productivity from employment gains
Xu (2013)[11]	Systematic review of Phase I clinical trials	B-cell CD19 cancers: NHL, B-ALL and CLL	Anti-CD19 CAR-modified T cells (scFv-CD137-CD3, scFv-CD28-CD3 and scFv-CD3) No comparator	5 studies (N=29) 12 NHL, 15 CLL, 2 B-ALL)	Pooled rates of AEs in Phase I trials: Fever 50% Rigors 40% Chills 30% Diarrhoea 15% Hypoxaemia, dyspnoea 20% Hypotension and capillary leak syndrome 45% Acute renal failure 25%	Pooled results: CR: 15% PFS at 6 months: 50.0% ± 9.9% PFS at 1 year: 18.5% ± 9.8%	Not assessed

Source/ID	Design	Condition/ indication	Comparison	N studies (patients)	Safety	Efficacy	Cost-effectiveness
Zhang (2015)[12]	Meta-analysis of Phase I clinical trials	Refractory B-cell haematologic cancers: CLL, ALL and other indolent lymphomas	Anti-CD19 CAR-modified T cells No comparator	14 studies (N=119)	Not meta-analysed. Paper provides narrative summary in discussion	Pooled response rates across Phase I trials (95% CI): B-ALL 93% (63–100%) B-CLL 62% (27–93%) B-lymphomas 36% (1–83%)	Not assessed
Zhu (2016)[13]	Systematic review of reported Phase I clinical trials	B-cell CD19 cancers Only data from CLL and NHL (not ALL) extracted for primary outcome	Anti-CD19 CAR-modified T cells (scFv-41BB-CD3, scFv-CD28-CD3 and scFv-CD3) No comparator	6 studies (N=50)	AEs in 10+ % of patients across pooled Phase I trials — all associated with CRS, TLS, B-cell depletion, and/or infection: Fever 54% Hypotension 26% Rigor 16% Fatigue, bacteraemia 14% Chill, dyspnoea, headache 12% Acute kidney injury, capillary leak syndrome, neutropenia 10%	Pooled results of Phase I trials: CR 24% PFS at 6 months: 43% PFS at 1 year: 27%	Not assessed

Abbreviations used in table: AE, adverse event; Axi-Cel, axicabtagene ciloleucel; B-ALL, B-cell acute lymphoblastic leukaemia; B-CLL, B-cell chronic lymphocytic leukaemia; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; EMA, European Medicines Agency; EU, European Union; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat population; IVIG, intravenous immunoglobulins; NHL, non-Hodgkin's lymphoma; NOS, not otherwise specified; ORR, overall response rate; QALY, quality-adjusted life-year; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; SCT, stem cell transplant; TLS, tumour lysis syndrome; TFL, transformed follicular lymphoma

Safety, efficacy and cost of CAR T-cell therapy delivered within a regulatory framework — plans for post-approval monitoring (Research Question 2)

Source/ID	Therapy	Country/ approval	Condition/ indication	Description	Status	Key results
EMA press release	Tisagenlecleucel	EU, EMA, 2018	B-ALL, refractory or in second line or later relapse (children/young adults) DLBCL, after 2+ lines of systemic therapy (adults)	1. Post-authorisation safety study (PASS): Non-interventional regular follow-up until December 2038 (B-ALL and DLBCL) 2. Post-authorisation efficacy study (PAES): In patients below 3 years of age annual reporting required until Dec 2023 (B-ALL) or 2022 (DLBCL) 3. Periodic safety update reports (PSURs) 4. Qualification of registry data	Planned, to be implemented when full licence is granted (currently has positive opinion)	None. First safety update due after six months
EMA press release	Axicabtagene ciloleucel	EU, EMA, 2018	DLBCL and PMBCL after 2+ lines of systemic therapy (adults)	1. Post-authorisation safety study (PASS): Non-interventional regular follow-up until Dec 2038 2. Periodic safety update reports (PSURS) 3. Qualification of patient registry	To be implemented when full licence is granted (currently has positive opinion)	None. First safety update due after six months
FDA pilot Clinical Safety Project[46]	CAR T-cell therapies	US, FDA, 2017	No limits stated	Central FDA-held database of safety information from multiple sponsors of CAR T-cell therapies, to monitor safety across classes and inform future approvals	Pilot underway	No results available
FDA post-marketing study[53]	Axicabtagene ciloleucel	US, FDA, 2017	DLBCL	Post-marketing observational study to primarily assess long-term toxicities	Unknown	None found
FDA post-marketing study[54]	Tisagenlecleucel	US, FDA, 2017	Childhood ALL and adult DLBCL	B2401 will include short-term CRS, neurologic and other adverse event reporting as well as long-term observational follow-up for the potential of second malignancy. N = 1000 ALL; and N = 1500 DLBCL	Underway	None found

Abbreviations used in table: B-ALL, B-cell acute lymphoblastic leukaemia; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; EU, European Union; QALY, quality-adjusted life-year; PMBCL, primary mediastinal large B-cell lymphoma; TFL, transformed follicular lymphoma

APPENDIX 7: Published overviews of the CAR T-cell clinical trial landscape (Research Question 3)

Source/ID	Condition	Purpose and inclusion criteria	Studies identified	Descriptive results
Hartmann (2017)[61, 63]	All	Overview of all documented trials published or underway by end of 2016 Includes trial characteristics and factors influencing translation to clinic	211	• 133 studies in haematologic malignancies, 78 in solid tumours • Clear focus on CD19-CAR T cells for B-cell malignancies; 23 published trials with most patients achieving complete or partial remission • Clinical benefit less pronounced in non-CD19-targeted haematologic malignancies and solid tumours • CAR T-cell therapy toxicity ranges from mild to life-threatening, including CRS, neurotoxicity, TLS, anaphylaxis, and on-target/off-tumour recognition • Factors influencing translation to clinic include: target choice, design of CAR construct, vector choice, starting material and handling, preconditioning regimen, administration
Holzinger (2016)[59]	All	Overview of all documented trials published or underway at beginning of 2016 Includes technical and clinical considerations for implementation	100+	• 74 conducted in the US, 27 in China, 4 in Europe, 1 in Japan, 1 in Australia • Majority of published and ongoing early-phase trials are in B-cell malignancies (including ALL and CLL), with favourable but variable outcomes • Factors to consider in the application of CAR T-cell therapy to solid cancers: disease status, tumour burden, target antigen, immune repression in tumour tissue, CAR T-cell infiltration, recruitment and activation of other pro-inflammatory and repressor immune cells • Direct comparison of the outcomes is difficult to make due to a number of technical and design variations, including the CAR composition, production and amplification of CAR T cells, patient preconditioning and cytokine support, CAR T-cell dose and other variations[11] • Lymphodepletion and CAR T-cell dose key factors for favourable prognosis; IL-2 co-administration is not recommended[12] • Phase I trials explore possibility of ruling out on-target/off-tumour autoreactivity of CAR T-cells towards healthy tissue; produced a lasting depletion of healthy B cells in CD19-targeted trials • CD19 target is common, others include CD20, CD22, Igk, and B-cell maturation protein BCMA • Summarises strategies being developed to reduce toxicity (suicide genes, dosing strategies) and increase tumour selectivity

Pettitt (2018)[62]	All	Overivew of the published clinical trial landscape including cancer indications, intervention details, outcomes and AEs studied, biases, and critical factors for implementation	20	• Small, prospective, uncontrolled trials; average number of patients 11 (range 1–30) • 17 conducted in US, 2 in China, 1 in Netherlands • CD19 antigen most common, but 8 others studied • Dosage ranged across studies but used standard units of cells per kilogram • Leukaemia then lymphoma most commonly studied; others include glioblastoma, sarcoma, seminal vesicle cancer, pancreatic adenocarcinoma, and pleural mesothelioma • Most studies use autologous cell source (from patient) • Cell expansion, persistence and safety reported fairly consistency, but efficacy heterogenous across disease indications and methodologies • Implementation challenges: technical considerations for CAR T-cell development, manufacturing practicability, clinical trial approaches, CAR T-cell quality and persistence, and patient management

Abbreviations used in table: B-ALL, B-cell acute lymphoblastic leukaemia; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; EU, European Union; QALY, quality-adjusted life-year; PMBCL, primary mediastinal large B-cell lymphoma; TFL, transformed follicular lymphoma