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An assessment of the post-approval challenges of autologous CAR-T therapy delivery: A Systematic review protocol

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Keywords: CAR-T, post-approval challenges, supply chain, capacity planning

ABSTRACT

Introduction: With recent regulatory approvals of two chimeric antigen receptor T-cell (CAR-T) therapies, the field now faces a number of post-approval challenges. These challenges are in some respects defined, and in others, uncertain due to the nascence of the field. At present, information pertaining to such post-approval challenges are scattered in various previous reviews or raised in singular papers reporting experience in working with the therapy. This systematic review is designed to analyse the post-approval challenges for robust delivery of CAR-T therapies to inform future work on the optimisation of CAR-T delivery to patients.

Methods and analysis: We will search Medline, EMBASE (OvidSP), BIOSIS & Web of Science, Cochrane Library & HEED, EconLit (ProQuest), WHOLIS WHO Library Database, PAIS International (ProQuest), Scopus for studies published between 2013 and 2018. In addition, a Google search for grey literature such as bioprocess blog posts, opinion pieces, press releases and listed companies involved in CAR-T development annual reports will be conducted. Two authors will independently screen the titles and abstracts identified from the search and accept or reject the studies according to the study inclusion criteria and any discrepancies will be discussed and resolved. The quality of the selected literature will be assessed using the CASP Systematic Review checklist. Data from eligible publications will be categorized using a flowchart and extracted using a data abstraction form. An analysis of the post-approval challenges of CAR-T therapies will be conducted.

Ethics and dissemination: This study does not require ethical review. The executed study conducted later will be published in a peer-reviewed journal in accordance with PRISMA guidelines. The findings from this review will be used to inform the development of an optimisation model for robust delivery of CAR-T therapies using a systems engineering approach.

Registration: This protocol will be submitted on PROSPERO.

STRENGTHS AND LIMITATIONS OF STUDY

- Only two approved products in 2017 make for relatively short-term and limited experiences with post-approval challenges
- Annual reports of listed companies are not peer-reviewed but strictly regulated by relevant stock exchange
- Only publicly listed companies that disclose their perceived risks are considered in this review hence there may be bias to larger companies' perspectives

BACKGROUND

Since the first reports of successes of using chimeric antigen receptor T-cell (CAR-T) to treat advanced leukemia in 2011(1,2), the field has grown expansively with over 400 trials listed on clinicaltrials.gov as of February 2018. The year 2017 saw the approvals of two of such therapies, Kymriah (Novartis, Basel Switzerland) for the treatment of patients up to 25 years of age with B-cell relapsed/refractory acute lymphoblastic leukemia (ALL)(3) and Yescarta (Kite, acquired by Gilead) for treatment of adult patients with relapsed or refractory large B-cell lymphoma(4). The regulatory framework currently can allow rapid approval of CAR-T for niche indications through various acceleration schemes but regulatory approval is but the beginning to another array of challenges facing companies.

For the case of Kymriah, the therapy was granted orphan designation, rare paediatric disease designation, fast track designation, and Breakthrough Therapy designation which was awarded only around one month after initial submission. Figure 1 shows the development and regulatory timeline of Kymriah. Breakthrough therapy designation allowed BLA data to be submitted as it was accumulated, instead of in a single bolus upon completion of pivotal clinical trials as part of a Biological Licensing Application (BLA) as usually required by conventional FDA approval pathways and hence allow faster regulatory approval. In this case study, the regulatory process was sped up from the conventional 10-month average from date of initial BLA submission to just 6 months.

With regulatory approval, there are still plenty of challenges that hinder patients from receiving these life-saving treatments and companies from providing them in a robust manner. A retrospective review on commercialized cell therapy products conducted by Dodson et al(5) categorized the translational challenges of cell therapies into pre-market, post-market, and manufacturing challenges that start pre-market and continue into the post-market phase. Table 1 provides a summary of the challenges as mentioned in various previous reviews.

"Pre-market challenges" covers challenges incurred in pre-clinical and clinical research up until market approval. Various previous studies have looked into the clinical development of CAR-T. Liu et al summarized the target antigen, indications, CAR and vectors chosen for registered clinical trials in China(6). Whilst the study provides useful insights on the distribution and trends in CAR-T clinical trials in China, it did not critically appraise the safety and efficacy of CAR-T treatments nor did it address the state of development of the CAR-T industry. Pettitt et al systematically and qualitatively assessed the CAR-T clinical trial landscape, providing insights on the cell source and type, CAR, indication, number of participants, adverse events and outcomes, safety and efficacy of CAR-T treatments(7). Hartman et al summarized the drivers in CAR-T clinical trial from target choice to administration and toxicity and efficacy as well as the regulatory hurdles associated to clinical translation of CAR-T cells.(8) These reviews reiterate the clinical importance of CAR-T as an effective anti-cancer treatment mainly for haematological malignancies and reiterated the importance of post-approval surveillance for long-term safety and efficacy.

"Post-market challenges" include establishing reimbursement models and encouraging clinical adoption(5), as well as institutional challenges surrounding the delivery of the therapy(9) and long-term safety(10). A quantitative review published recently conducted a multi-stakeholder and multi-national assessment focussed on the barriers to the adoption of cell therapies, but not specific to CAR-T(11). Specific to CAR-T, Mcguirk et al(9) discussed the institutional challenges from cell extraction (leukapheresis) to administration of the therapy and post-operative management and monitoring from their experience at the University of Kansas Medical Centre with Novartis' CTL019 (Kymriah). A well-trained multi-disciplinary team and associated infrastructure presents itself as a constraint to successful and timely delivery of CAR-T.

"Manufacturing challenges" for CAR-T therapies are very well researched and reviewed(12–14). Levine et al(13) details the UPenn and Novartis approach to manufacturing of CAR-T. Vormittag et al(12) reviewed the manufacturing technologies used in published clinical trials and summarised the commonly used equipment and manufacturing routes. Robust supply of all raw materials and consumables is important for the overall supply chain robustness. Brindley et al(15) mentioned the limitation of availability of serum in 2012 and viral vectors supplies are strained according to MacRae 2018(16).

Public-private partnership and contracts signed for patents etc. were reviewed by Goldman et al 2017(17). The review was focused mostly on private-public partnerships, evaluating the collaborative research, technology licensing and some service agreements between companies and academic centres. However, as the products get commercialized, collaborations are slowly shifting towards company-to-company agreements for services such as contract manufacturing.

As products are getting past regulatory approval, more emphasis should be put on addressing post-approval challenges to allow successful commercialization. A comprehensive investigation into the challenges (e.g. raw material supply pain points, supply chain, institutional challenges) for the delivery of autologous CAR-T can provide new insights into the overall process robustness from collection to post-administration of the therapy (i.e. the process's ability of successfully delivering the therapy under varying conditions(18)).

Table 1 Table showing the challenges in the commercialization of CAR-T therapies, table structure as adapted from Dodson et al.

Pre-market	Post market
(a) Product development - Technical considerations (e.g. cell source, CAR construct, costimulatory domain) (6,7) - Manufacturing practicability[7] - CAR-T cell quality and persistence [7] (b) Clinical trials - Clinical trial approaches [7] - Enrolment and patient management [7] (c) Safety, efficacy and adverse event management[7.]	(a) Long-term safety uncertainties(10) (b) Institutional preparation - Training and education of care team and patients(9) and clinical haematologists(19) - Emergency department and intensive care unit(9) - Side effects management(9) (c) Reimbursement(11,20) (d) Clinical adoption(11) (e) Regulatory compliance, e.g. post-approval process changes(21)
Manufacturing	
(a) Manufacturing technologies(12–14) (b) Manufacturing models(22,23) (c) Supply chain (d) Raw material supply (e.g. serum(15), viral vectors(16)) (e) Capacity planning decisions (i.e. partnership, in-house, outsource)	

AIMS & OBJECTIVES

This systematic review aims to identify: (1) Key post-approval challenges of CAR-T therapies addressed in published literature; (2) Risks and concerns relating to delivery of CAR-T from the perspective of suppliers. These are critical in better understanding the constraints in the current delivery routine and identify the optimisation targets for future work on improving the robustness of delivery of CAR-T therapies through a systems engineering approach.

KEY RESEARCH QUESTIONS

1. Primary research questions: What are the post-approval challenges for delivery of CAR-T therapies? What are the main concerns of CAR-T suppliers?

2. Secondary question: What has to be optimised and what are the constraints in robust delivery of CAR-T therapies?

METHODS

This systematic review will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P 2015) statement, which for this protocol is specified in Appendix 1(24).

Eligibility criteria

Table 2 shows the inclusion and exclusion criteria for this study. As the field is moving is a very fast pace, only English publications published within the last 5 years are included in this study. The earliest approval for CAR-T is in August 2017 hence the publications too long before are unlikely to be relevant. Only papers that look into post-approval commercialization challenges supply chain, delivery and clinical use are included in order to omit irrelevant and generic challenges.

Early research papers on cellular level interactions and biology and clinical trials are considerations important for regulatory approval, hence irrelevant for post-approval challenges and hence excluded to ensure relevance.

Due to the nature of this study which looks at the post-approval challenges, a topic mostly discussed in industry and less so in academia, grey literature is an important source of latest trends and updated information. To avoid bias in the grey literature search, sources sponsored by manufacturers and suppliers will be excluded.

Table 2 Inclusion and exclusion criteria for the study

Inclusion criteria	Exclusion criteria
- Published within the last 5 years - English language publications - CAR-T related - Identified experiences in product supply chain, delivery and clinical use - Identified challenges in product supply chain, delivery and clinical use	- Non-English language publications - Papers with exclusive focus on CAR-T basic research - Clinical trials studies - Technical papers with exclusive focus on bioprocess and manufacturing - Papers that focus on pre-approval challenges such as regulatory approval hurdles - Competing interests – sponsored by manufacturer

Search strategy

The following databases will be searched: Medline, EMBASE (OvidSP), BIOSIS & Web of Science, Cochrane Library & HEED, EconLit (ProQuest), WHOLIS WHO Library Database, PAIS International (ProQuest), Scopus. In addition, a Google search for grey literature such as bioprocess blog posts, opinion pieces, press releases and listed companies involved in CAR-T development annual reports will be conducted. Search terms in Table 3 are developed around the CAR-T process from collection to delivery. The themes are designed according to the roadmap for cost of good planning in cell therapy proposed by Lipsitz et al(25).

Table 3 Themes and search term development

Theme	Search term/string: ***((CAR-T) OR chimeric antigen receptor) AND + following keywords***
Tissue procurement	*collection OR acquisition, *apheresis, variability*
Material acquisition	*Bioequivalence, consistency, comparability*
Facility operation	*demand, scale, capacity, outsourcing, *centralised*
Production	*GMP, schedul*, quality control, personnel*
Distribution	*Packaging, distribution, logistics, traceability*
Patient administration	*Institutional, long term safety, clinician*

In addition to the above search strings, to understand the post-marketing challenges of the two approved products that have been reported, the following search, which is limited to literature found between the approval date and present, is conducted and shown in Table 4:

Table 4 Additional search for approved CAR-T products

Product	Custom date range
(Kymriah OR tisagenlecleucel)	1 Sep 2017 – 1 Aug 2018
(Yescarta OR axicabtagene ciloleucel)	19 Oct 2017 – 1 Aug 2018

Study selection

Two independent reviewers will conduct the literature search according to this protocol. The manuscript title and abstracts will be screened and eligibility determined independently by each reviewer. Valid studies will be assessed for their quality before any extraction of information. Any discrepancies that arise between the reviewers will be discussed until consensus is reached.

Quality assessment and risk of bias

Two reviewers will independently check each article to minimize bias using the Collaboration's risk of bias tool as described in the Cochrane Handbook for Systematic Review of Interventions.(26). All selected articles will be judged for their quality based on the CASP systematic review checklist(27) and data analysis.

Data extraction

Eligible sources will subsequently be reviewed in detail and key relevant challenges will be extracted and categorized into nine domains from the post-market and manufacturing challenges in Table 1:

1. Manufacturing (technologies and models)
2. Supply chain
3. Raw material supply
4. Capacity planning decisions
5. Long-term safety uncertainties
6. Institutional preparations
7. Reimbursement
8. Clinical adoption
9. Regulatory compliance

The identified challenges are then classified into (1) Constraint; (2) Optimization target; (3) Risk. Figure 2 shows the method of categorization of the challenges identified and the data to extract if available. To provide some illustrative examples, shelf-life of the product can be identified as a constraint, and the product must be administered to patient within *x* hours after formulation (range and limit); batch failure can be identified as a risk with *x%* risk of occurrence and consequence of batch loss; Utilization rate of resources such as personnel, equipment and cleanroom space can be identified can a potential optimization target to allow the overall system to become more resource-efficient.

The data will be categorized and extracted and recorded into a predesigned Excel database by each reviewer independently. Any discrepancies will be discussed until consensus is reached. This data will lay basis for the formulation of a problem statement for future optimization tools.

Patient and Public Involvement

This systematic review of published and grey literature does not directly involve patients.

Ethics and dissemination

Due to the use of the publicly available, published data, this study will not require an ethical approval. The executed study conducted later in the year will be published in a peer-reviewed journal in accordance with PRISMA guidelines. Any deviations in the execution shall be noted in the subsequent systematic review publication. The findings from this review will be used to inform the development of an optimisation model for robust delivery of CAR-T therapies using a systems engineering approach.

Acknowledgments

David Williams and Brock Reeve provided review and commentary on the paper themes.

Contributorship statement

CL conceptualized and wrote the manuscript. EM provided systematic review expertise, assisted in the development of the protocol methodology and revised the first draft. CLHH and AC revised the first draft. AY provided valuable systems engineering expertise for the development of the methods and amendments for clarity. DB, AY and ZFC edited for relevance and clarity and are the senior guarantying authors. All authors read and approved the final manuscript. All authors completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. There are no relevant conflicts of interest, financial or other types of relationships that may influence the manuscript declared by authors. Authors do not have any patents and are not associated to any conditions or circumstances that may lead to conflicts of interest.

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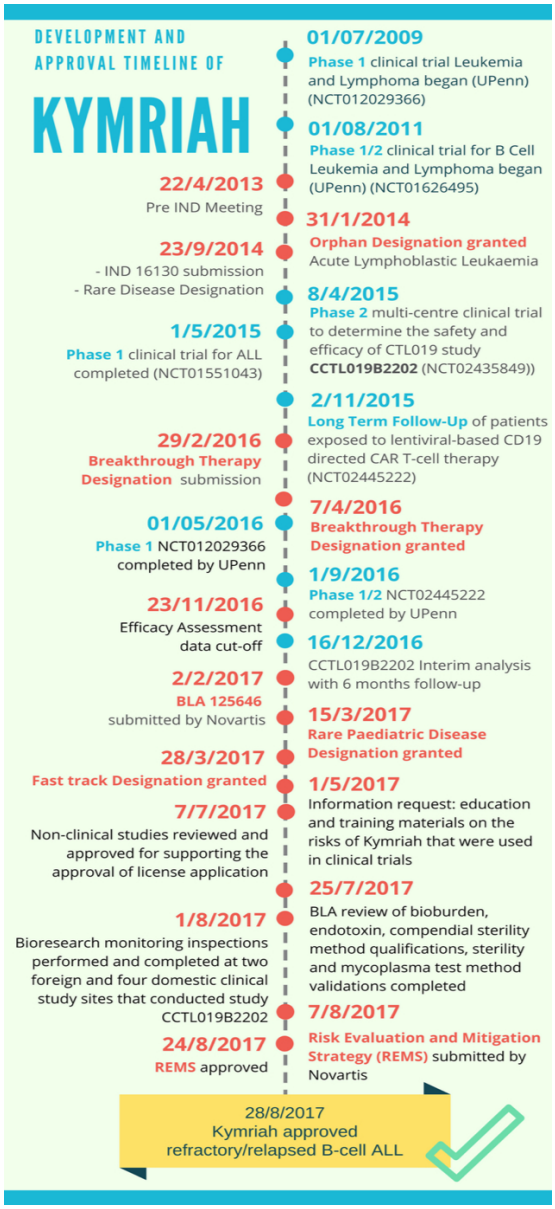

Figure 1: Development and approval timeline for Kymriah

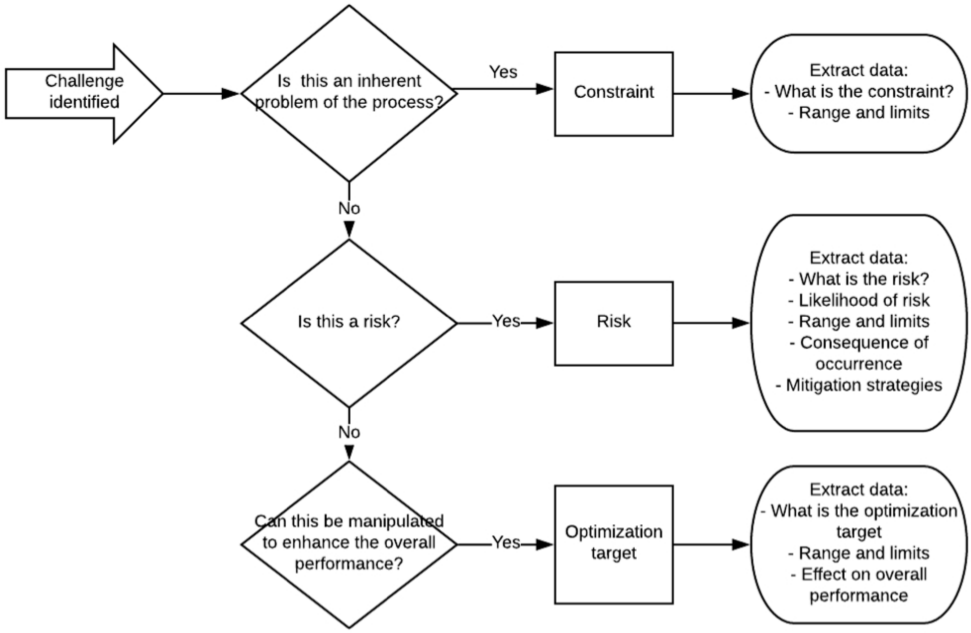

Figure 2: Schematic showing the categorization and data extraction method

Appendix 1: PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☒	N/A
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-15
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	213-222
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	223-230
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	223-230
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	223-230
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	74-119
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	129-133
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	138-150
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	153-155
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	162
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	199-202

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	169-173
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	199-202
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	182-193
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	191-198
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	174-178
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	181-201
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	199-201
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	174-178
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	177

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Systematic review protocol: An assessment of the post-approval challenges of autologous CAR-T therapy delivery

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Abstract

Introduction: Following recent regulatory approvals of two chimeric antigen receptor T-cell (CAR-T) therapies, the field now faces a number of post-approval challenges. These challenges are in some respects defined and, in others, uncertain due to the nascence of the field. At present, information pertaining to such post-approval challenges are scattered in various previous reviews or raised in singular papers reporting experience in working with the therapy. This systematic review is designed to evaluate and summarise the post-approval challenges for robust delivery of CAR-T therapies to inform future work on the optimisation of CAR-T delivery to patients.

Methods and analysis: We will search Medline, EMBASE (OvidSP), BIOSIS & Web of Science, Cochrane Library, ICER database, NICE Evidence Search, CEA Registry, WHOLIS WHO Library and Scopus for studies published between 2014 and the present. In addition, a Google search for grey literature such as bioprocess blog posts, opinion pieces, press releases and listed companies involved in CAR-T development annual reports will be conducted. Two authors will independently screen the titles and abstracts identified from the search and accept or reject the studies according to the study inclusion criteria and any discrepancies will be discussed and resolved. The quality of the selected literature will be assessed using the CASP Systematic Review checklist and grey literature will be assessed using the AACODS checklist. Data from eligible publications will be categorized using a flowchart and extracted using a data abstraction form. Qualitative and quantitative analysis of the post-approval challenges of CAR-T therapies will be conducted based on the results attained.

Ethics and dissemination: The executed study will be published in a peer-reviewed journal in accordance with PRISMA guidelines. The findings from this review will be used to inform the development of an optimisation model for robust delivery of CAR-T therapies using a systems engineering approach.

PROSPERO Registration Number: CRD42018109756

Keywords

CAR-T, post-approval challenges, supply chain, capacity planning

Strengths and Limitations

- Only two approved products in 2017 make for relatively short-term and limited experiences with post-approval challenges.
- Annual reports of listed companies are not peer-reviewed but strictly regulated by relevant stock exchange.
- Only publicly listed companies that disclose their perceived risks are considered in this review hence there may be bias to larger companies' perspectives.
- Limiting to studies only of the English language may cause bias in the grey literature search. However, as both products have only been approved in English-speaking countries, the bias is relatively less significant.

Background

Since the first reports of successes of using chimeric antigen receptor T-cell (CAR-T) to treat advanced leukaemia in 2011[1,2], the field has grown expansively with over 400 trials listed on clinicaltrials.gov as of February 2018. The year 2017 saw the approvals of two of such therapies, Kymriah (Novartis, Basel, Switzerland) for the treatment of patients of up to 25 years of age with B-cell relapsed/refractory acute lymphoblastic leukaemia (ALL)[3] and Yescarta (Kite, acquired by Gilead) for treatment of adult patients with relapsed or refractory large B-cell lymphoma[4]. The regulatory framework currently can allow rapid approval of CAR-T for niche indications through various acceleration schemes but regulatory approval is but the beginning of another array of challenges facing companies.

In the case of Kymriah, the therapy was granted orphan designation, rare paediatric disease designation, fast track designation, and Breakthrough Therapy designation which was awarded only around one month after initial submission. Figure 1 shows the development and regulatory timeline of Kymriah. Breakthrough therapy designation allowed BLA data to be submitted as it was accumulated, instead of in a single bolus upon completion of pivotal clinical trials as part of a Biological Licensing Application (BLA) as usually required by conventional FDA approval pathways and hence allow faster regulatory approval. In this case study, the regulatory process was accelerated from the conventional 10-month average from date of initial BLA submission to just 6 months.

With regulatory approval, there are still plenty of challenges that hinder patients from receiving these life-saving treatments and companies from providing them in a robust manner. A retrospective review on commercialized cell therapy products conducted by Dodson et al[5] categorized the translational challenges of cell therapies into pre-market, post-market, and manufacturing challenges that start pre-market and continue into the post-market phase. Table 1 provides a summary of the challenges as mentioned in various previous reviews.

"Pre-market challenges" covers challenges incurred in pre-clinical and clinical research up until market approval. Various prior studies have looked into the clinical development of CAR-T. Liu et al summarized the target antigen, indications, CAR and vectors chosen for registered clinical trials in China[6]. Whilst the study provides useful insights on the distribution and trends in CAR-T clinical trials in China, it did not critically appraise the safety and efficacy of CAR-T treatments nor did it address the state of development of the CAR-T industry. Pettitt et al systematically and qualitatively assessed the CAR-T clinical trial landscape, providing insights on the cell source and type, CAR, indication, number of participants, adverse events and outcomes, safety and efficacy of CAR-T treatments[7]. Hartman et al summarized the drivers in CAR-T clinical trial from target choice to administration and toxicity and efficacy as well as the regulatory hurdles associated to clinical translation of CAR-T cells.[8] These reviews reiterate the clinical importance of CAR-T as an effective anti-cancer treatment mainly for haematological malignancies and reiterated the importance of post-approval surveillance for long-term safety and efficacy.

"Post-market challenges" include establishing reimbursement models and encouraging clinical adoption[5], as well as institutional challenges surrounding the delivery of the therapy[9] and long-term

safety[10]. A quantitative review published recently conducted a multi-stakeholder and multi-national assessment focussed on the barriers to the adoption of cell therapies, but not specific to CAR-T[11]. Specific to CAR-T, Mcguirk et al[9] discussed the institutional challenges from cell extraction (leukapheresis) to administration of the therapy and post-operative management and monitoring from their experience at the University of Kansas Medical Centre with Novartis' CTL019 (Kymriah). A well-trained multi-disciplinary team and associated infrastructure presents itself as a constraint to successful and timely delivery of CAR-T.

"Manufacturing challenges" for CAR-T therapies are very well researched and reviewed[12–14]. Levine et al[13] details the UPenn and Novartis approach to manufacturing of CAR-T. Vormittag et al[12] reviewed the manufacturing technologies used in published clinical trials and summarised the commonly used equipment and manufacturing routes. Robust supply of all raw materials and consumables is important for the overall supply chain robustness. Brindley et al[15] mentioned the limitation of availability of serum in 2012 and viral vectors supplies are strained according to MacRae 2018[16].

Public-private partnership and contracts signed for patents etc. were reviewed by Goldman et al 2017[17]. The review was focused mostly on private-public partnerships, evaluating the collaborative research, technology licensing and some service agreements between companies and academic centres. However, as the products get commercialized, collaborations are slowly shifting towards company-to-company agreements for services such as contract manufacturing.

As products are getting past regulatory approval, more emphasis should be put on addressing post-approval challenges to allow for successful commercialization. A comprehensive investigation into the challenges (e.g. raw material supply pain points, supply chain, institutional challenges) for the delivery of autologous CAR-T can provide new insights into the overall process robustness from collection to post-administration of the therapy (i.e. the process's ability to deliver successfully the therapy under varying conditions[18]).

Table 1 Table showing the challenges in the commercialization of CAR-T therapies, table structure as adapted from Dodson et al.

Pre-market	Post market
(a) Product development - Technical considerations (e.g. cell source, CAR construct, costimulatory domain) [6,7] - Manufacturing practicability[7] - CAR-T cell quality and persistence [7] (b) Clinical trials - Clinical trial approaches [7] - Enrolment and patient management [7] (c) Safety, efficacy and adverse event management[7].	(a) Long-term safety uncertainties[10] (b) Institutional preparation - Training and education of care team and patients[9] and clinical haematologists[19] - Emergency department and intensive care unit[9] - Side effects management[9] (c) Reimbursement[11,20] (d) Clinical adoption[11] (e) Regulatory compliance, e.g. post-approval process changes[21]
Manufacturing	
(a) Manufacturing technologies[12–14] (b) Manufacturing models[22,23] (c) Supply chain (d) Raw material supply (e.g. serum[15], viral vectors[16]) (e) Capacity planning decisions (i.e. partnership, in-house, outsource)	

Objectives

This systematic review aims to identify: (1) Key post-approval challenges of CAR-T therapies addressed in published literature; (2) Risks and concerns relating to delivery of CAR-T from the perspective of suppliers. These are critical in better understanding the constraints in the current delivery routine and identify the optimisation targets for future work on improving the robustness of delivery of CAR-T therapies through a systems engineering approach.

Key research questions

1. Primary research questions: What are the post-approval challenges for delivery of CAR-T therapies? What are the main concerns of CAR-T suppliers?
2. Secondary question: What has to be optimised and what are the constraints in robust delivery of CAR-T therapies?

Methods and Analysis

This systematic review will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix 1) [24].

Eligibility criteria

Table 2 shows the inclusion and exclusion criteria for this study. As the field is moving at a very fast pace, only English publications published within the last 5 years are included in this study. The earliest approval for CAR-T is in August 2017, hence publications dating from long before this date are unlikely to be relevant. Only papers that look into post-approval commercialization challenges – supply chain, delivery and clinical use – are included in order to omit irrelevant and generic challenges.

Early research papers on cellular level interactions and biology and clinical trials are considerations important for regulatory approval, hence irrelevant for post-approval challenges and hence excluded to ensure relevance.

Due to the nature of this study which looks at the post-approval challenges, a topic mostly discussed in industry and less so in academia, grey literature is an important source of the latest trends and updated information. To avoid bias in the grey literature search, sources sponsored by manufacturers and suppliers will be excluded.

Table 2 Inclusion and exclusion criteria for the study

Inclusion criteria	Exclusion criteria
- Published within the last 5 years - English language publications - CAR-T related - Identified experiences in product supply chain, delivery and clinical use - Identified challenges in product supply chain, delivery and clinical use	- Non-English language publications - Papers with exclusive focus on CAR-T basic research - Clinical trials studies - Technical papers with exclusive focus on bioprocess and manufacturing - Papers that focus on pre-approval challenges such as regulatory approval hurdles - Competing interests – sponsored by manufacturer

Search strategy

The following databases will be searched, and publications published between 1st January 2014 to present will be assessed: Medline, EMBASE (OvidSP), BIOSIS & Web of Science, Cochrane Library, ICER database, NICE Evidence Search, CEA Registry, WHOLIS WHO Library and Scopus. In addition, a Google search for grey literature such as bioprocess blog posts, opinion pieces, press releases and listed companies involved in CAR-T development annual reports will be conducted. Search terms in Table 3 are developed around the CAR-T process from collection to delivery. The themes are designed according to the roadmap for cost-of-goods planning in cell therapy proposed by Lipsitz et al[25].

Table 3 Themes and search term development

Theme	Search term/string: ***((CAR-T) OR chimeric antigen receptor) AND + following keywords***
Tissue procurement	*collection OR acquisition, *apheresis, variability*
Material acquisition	*Bioequivalence, consistency, comparability*
Facility operation	*demand, scale, capacity, outsourcing, *centralised*
Production	*GMP, schedul*, quality control, personnel*
Distribution	*Packaging, distribution, logistics, traceability*
Patient administration	*Institutional, long term safety, clinician*

In addition to the above search strings, to understand the post-marketing challenges of the two approved products that have been reported, the search as stipulated in Table 4, which is limited to literature found between the approval date and present, will be conducted.

Table 4: Custom date range for approved products

Product	Custom date range
(Kymriah OR tisagenlecleucel)	1 Sep 2017 – present
(Yescarta OR axicabtagene ciloleucel)	19 Oct 2017 – present

Study selection

Two independent reviewers will conduct the literature search according to this protocol. The manuscript title and abstracts will be screened, and eligibility determined independently by each reviewer. Valid studies will be assessed for their quality before any extraction of information. Any discrepancies that arise between the reviewers will be discussed until consensus is reached.

Quality assessment and risk of bias

Two reviewers will independently check each article to minimize bias using the Collaboration's risk of bias tool as described in the Cochrane Handbook for Systematic Review of Interventions.[26]. All selected articles will be judged for their quality based on the CASP systematic review checklist[27] and the quality of any grey literature will be further assessed using the AACODS checklist to grade the literature and ensure acceptable quality[28]. The AACODS checklist was specifically designed by Tyndall et al for evaluation and critical appraisal of grey literature and due to the potential inclusion of grey literature produced by government, business and industry, the checklist is especially relevant for this systematic review.

Data extraction

Eligible sources will subsequently be reviewed in detail and key relevant challenges will be extracted and categorized into nine domains from the post-market and manufacturing challenges in Table 1:

1. Manufacturing (technologies and models)
2. Supply chain
3. Raw material supply
4. Capacity planning decisions
5. Long-term safety uncertainties
6. Institutional preparations
7. Reimbursement
8. Clinical adoption
9. Regulatory compliance

Synthesis

The identified challenges are then classified into (1) Constraint; (2) Optimization target; (3) Risk. Figure 2 shows the method of categorization of the challenges identified and the data to extract if available. To provide some illustrative examples, shelf-life of the product can be identified as a constraint, and the product must be administered to patient within *x* hours after formulation (range and limit); batch failure can be identified as a risk with *x%* risk of occurrence and consequence of batch loss; Utilization rate of resources such as personnel, equipment and cleanroom space can be identified as a potential optimization target to allow the overall system to become more resource-efficient.

The data will be categorized and extracted and recorded into a predesigned Excel database by each reviewer independently. Any discrepancies will be discussed until consensus is reached. This data will lay the basis for the formulation of a problem statement for future optimization tools. Further to the data extraction, due to the heterogenous nature of the results from the preliminary analysis, a comprehensive review of the identified challenges will be qualitatively analysed to generate a narrative analysis of the post-approval challenges encountered by CAR-T commercialisation so far. If the results permit, a quantitative analysis will be conducted.

Ethics and Dissemination

Due to the use of the publicly available, published data, this study will not require an ethical approval. The executed study conducted later in the year will be published in a peer-reviewed journal in accordance with PRISMA guidelines. Any deviations in the execution shall be noted in the subsequent systematic review publication. The findings from this review will be used to inform the development of an optimisation model for robust delivery of CAR-T therapies using a systems engineering approach.

Patient and Public Involvement

This systematic review of published and grey literature does not directly involve patients.

List of Figures

Figure 1: Development and approval timeline for Kymriah (in blue: clinical trial related milestones; in red: regulatory related milestones)

Figure 2: Schematic showing the categorisation and data extraction method

Acknowledgements

David Williams and Brock Reeve provided review and commentary on the paper themes. We would also like to thank the Bodleian Radcliffe Science Library librarian, Alessandra Vetrugno and Bodleian Health Care Library librarian, Nia Roberts for their guidance in reviewing the search strategy proposed in this protocol.

Contributorship statement

CL conceptualized and wrote the manuscript. EM provided systematic review expertise and assisted in the development of the protocol methodology. AY provided valuable systems engineering expertise for the development of the methods and amendments for clarity. CLHH, DAB, ARC and ZFC edited for relevance and clarity and are the senior guarantying authors. All authors approved the final manuscript. All authors read and approved the final manuscript. All authors completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. There are no relevant conflicts of interest, financial or other types of relationships that may influence the manuscript declared by authors. Authors do not have any patents and are not associated to any conditions or circumstances that may lead to conflicts of interest.

Competing interests

None declared.

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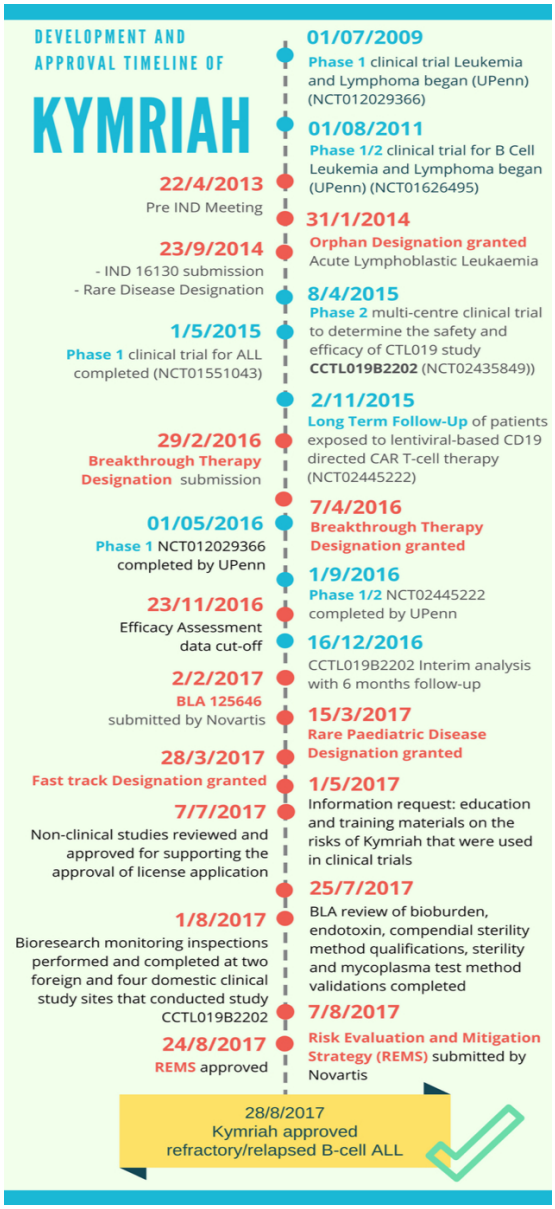

Figure 1: Development and approval timeline for Kymriah

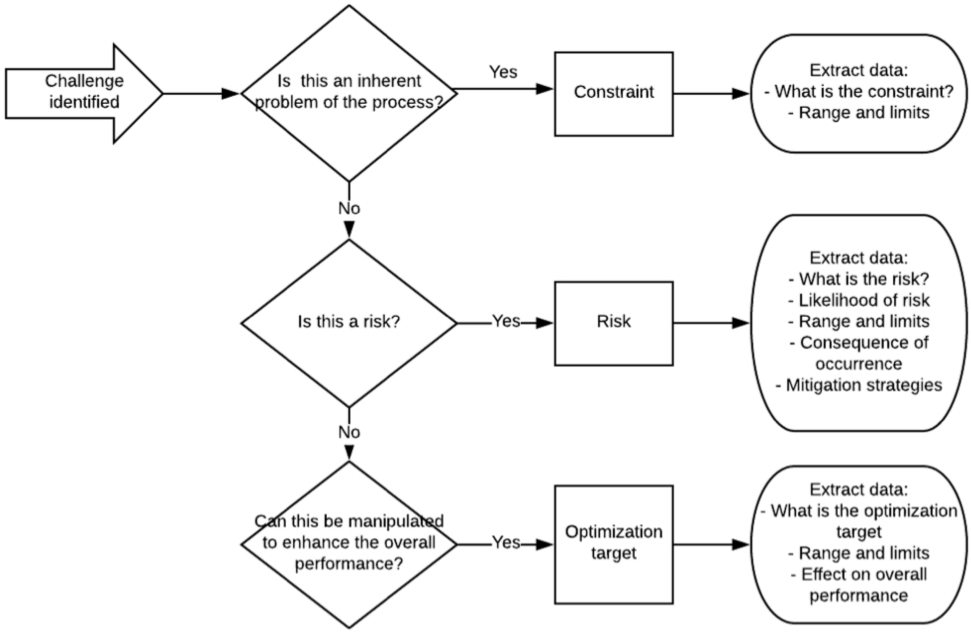

Figure 2: Schematic showing the categorisation and data extraction method

Appendix 1: PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☒	N/A
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-15
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	213-222
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	223-230
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	223-230
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	223-230
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	74-119
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	129-133
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	138-150
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	153-155
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	162
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	199-202

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	169-173
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	199-202
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	182-193
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	191-198
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	174-178
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	181-201
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	199-201
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	174-178
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	177