

## **Trial Component Specifications**

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### **Background**

In 2016 JPAC approved changes to Chapter 8 of the Red Book to make the process for approving a trial component specification clearer (JPAC 16-78). This text has been incorporated into the 9<sup>th</sup> Edition of the Red Book.

Recently it has become clear through a number of submissions to SACBC, that the term 'trial component specification' is confusing. In particular, its name suggests (by definition) that the component is being used as part of a clinical trial, which is not necessarily the case. The purpose of this document is to improve the definition of what a trial component specification is for, and how the degree of novelty of the proposed trial component impacts on the extent of validation required and any limitations on planned clinical use. Proposed changes to relevant sections of Chapter 8 of the Red Book are made at the end of the document to bring this in line with the content of the paper.

### **Current process**

Currently in Chapter 8 of the Red Book a trial component specification is used when there is a need to produce a component for clinical use on a temporary basis, and there is no clear need to produce it routinely. This occurs mainly for two reasons:

- 1) To undertake a clinical trial of a novel component as part of R+D (for example rejuvenated red cells)
- 2) Following completion of R+D by UKBTS or a manufacturer of a medical device, to undertake operational assessment of a component prior to UKBTS making a decision as to whether to produce the component on an ongoing basis (for example pathogen inactivated platelets)

### **When is a component novel?**

Currently whether a component is considered novel is determined by SACBC, based on review of information submitted to the committee, usually at the *end* of the validation process although advice may have been sought in advance [9<sup>th</sup> ed Ch8 Table 8.2].

By definition, if a component does not have an agreed specification in the Red Book it is novel. However, even if a component has an agreed specification, it could also be the case that it may be considered novel if its intended clinical use is out with current normal clinical practice/guidelines or requires a change to the specification.

It may be helpful for the future to consider the type of information that should be provided to SACBC prior to commencing validation work, as the degree of novelty of a trial component will impact on the extent of laboratory and clinical data that will need to be generated during validation stages and may also impact on the clinical use of the component.

The table below classifies trial components by degree of novelty (Low -Very High) based on the regulatory requirement and level of pre-existing clinical data. It is expected that as new component moves through the R+D pipeline, that the degree of novelty will reduce.

Questions that JPAC may consider when using the table above to determine whether a component is novel might include:

- What is the intended clinical use of the product, which patient groups and in the context of a trial or not?
- Is the product covered by an existing specification in the Red Book? If not, does it require a change to an existing specification or a trial component specification?
- Is the method that will be used to produce the component the same as that used in other countries where clinical data/use has been generated?
- Are there any areas of contention internationally, for example what the shelf-life should be?
- What is the extent of clinical use/data to date on efficacy/safety and is it sufficient to allow inclusion of the component on an ongoing basis?

As blood components included in the Red Book are produced using medical devices, these proposals cover and do not apply to blood products categorised as licenced medicines.

### **Validation**

In considering the extent of validation required to approve a trial component specification, the higher the degree of novelty then the more extensive the validation requirements are likely to be, linked to key consideration of likely level of risk to recipients. However, even for changes to standard components there is a requirement for UKBTS to validate any changes to production or usage. The extent of validation needs to be proportionate to the degree of novelty, and level of clinical risk. This must be taken on a case by case basis, and investigators are encouraged to submit validation plans to SACBC for advice prior to undertaking studies where data will then be submitted in due course for SACBC for review and approval.

### **Clinical use of component**

A further consideration for any group undertaking clinical research on novel components and developing a trial component specification is whether clinical use of the component constitutes a change in standard of care, or is a research study. Components in the medium and high degree of novelty category would almost certainly necessitate a research study (clinical trial), with usage limited to recipients included in the study. For components in the 'low' category, this is unlikely. However this needs to be assessed on a case by case basis based on the intended clinical use and review of laboratory/clinical data and use to date. It is the responsibility of the group intending to use the component to determine the intended clinical use, and to include information on this in the draft specification submitted to SACBC. Any trial component specification should include information regarding any limitations to the extent of clinical use, for example if there is a recommended maximum number of units transfused.

In line with other documents on the JPAC website there is a yearly review of trial component specifications as to whether amendments are needed, or the document should be removed as obsolete.

### **Proposed revised terminology**

In view of the confusing nature of the term 'trial component specification', which implies that the components will only be used as part of a clinical trial, it is proposed by SACBC that an alternative more flexible term is used throughout the Red Book. The suggested alternative term is 'Provisional component'.

**Table 1.** Degree of novelty of blood components at the point in time considered by SACBC

Degree of novelty	Regulatory	Clinical data/experience	Extent of laboratory validation required	Clinical use	Recent Examples
<b>Very high</b>	Produced using medical device/process that is <b>NOT</b> CE marked, or covered by manufacturer's IFU.  A notice of no objection from the MHRA would be required for any trial.	No clinical use in humans	Extensive laboratory validation and data in relevant animal models. Likely to have to define all key critical variables that determine product quality.	First in man/phase I studies. HRA approval required and not to be used outside of approved study.	Phase 1 studies of pathogen inactivated platelets
<b>High</b>	Produced using medical device that is <b>NOT</b> CE marked, or covered by manufacturer's IFU.  A notice of no objection from the MHRA would be required for any trial.	Clinical data likely to be limited to small scale studies as part of R+D, or historical use or use outside of Europe.	Extensive laboratory validation. Likely to have to further define some critical variables in product quality.	Likely to be a phase II/III research study. HRA approval required and not to be used outside of approved study.	Rejuvenation of red cells Pathogen Inactivation of red cells
<b>Medium</b>	Produced using medical device that is CE marked, but <b>OUTSIDE</b> of its intended use or manufacturer's instructions for use (IFU).  A notice of no objection from the MHRA would be required for any trial.	Clinical data likely to be limited to small scale studies as part of R+D or historical/small scale clinical use or use.	Laboratory validation required guided by data to date and intended use. Likely to have to validate changes to key variables such as temperature or duration of storage.	Likely to be a phase II/III research study. HRA approval required and not to be used outside of approved study.	Storage of platelets at 4°C
<b>Low</b>	Produced using medical device that is CE marked <b>WITHIN</b> its intended use & manufacturer's IFU.  Currently NO specification in Red Book or not for the usage proposed  Likely to be a specification for product elsewhere e.g Council of Europe or AABB guidelines.	Not used recently in UK, or change in clinical use of an existing component.  Might be in routine use elsewhere internationally but not the UK.	Extent of laboratory work guided by nature of change to be made and any uncertainties in published data e.g shelf-life.	Use might either be considered a change in clinical practice or as part of an approved research study, to be determined based on clinical usage/data to date. Use might be restricted in first instance to pilot sites. Safety might be monitored through haemovigilance which might be enhanced	Operational studies of Pathogen inactivation of platelets  LD Red cells and plasma

	<p>Use would not be precluded by content of BSQR or relevant EU directives.</p> <p>Use would require local validation and approval by SACBC/JPAC.</p>			above standard based on risk.	
<p><b>Standard component (therefore not a 'trial specification')</b></p>	<p>Produced using medical device that is CE marked <b>WITHIN</b> its intended use &amp; manufacturer's IFU.</p> <p>Has <b>APPROVED</b> specification in Red Book.</p> <p>In routine use in the UK and manufactured to approved specification in Red Book.</p>	<p>Widespread clinical experience from routine use in the UK and elsewhere</p>	<p>Introduction would require local validation.</p>	<p>As per clinical guidelines</p>	