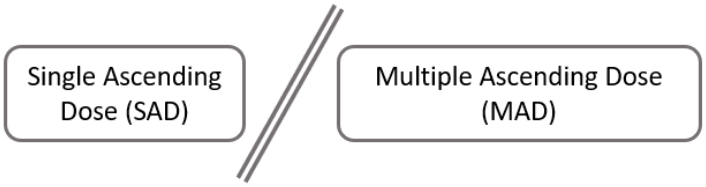
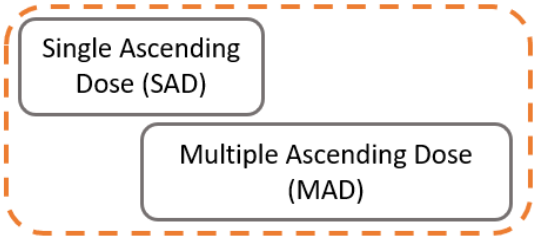
The purpose of this education document is to outline the ethical aspects considered by Bellberry HRECs when reviewing multi-stage Phase 1 trials.

In traditional Single Ascending Dose (SAD)–Multiple Ascending Dose (MAD) study design, the SAD and MAD study stages were typically sequential and often conducted as two separate protocols[1]. In this trial structure, the MAD stage is not initiated until the SAD stage has been completed. The SAD portion of work establishes a maximum tolerated dose (MTD) and seeks to reach the maximum planned dose without observation of dose limiting toxicities.

In more recent times, SAD-MAD investigations are often presented as a single, combined SAD-MAD protocol, and conducted as a single Protocol.

These combined SAD-MAD protocols can be presented as either sequential phases of activity[2], or overlapping phases of activity where the SAD and MAD components integrate with each other[3]. In overlapping or integrated SAD-MAD studies, the MAD stage may be initiated before completion of the SAD phase of investigation. In these overlapping structures, it is important to identify which SAD doses "unlock" the corresponding MAD cohort.

(1) Traditional SAD/MAD study design (2 protocols)	
Combined SAD/MAD study (sequential phases in a combined protocol)	
Combined SAD/MAD study (integrated phases in a combined protocol)	

Bellberry recognises, reviews and (where appropriate) approves Phase 1 studies using traditional, combined, sequential and overlapping/integrated study designs. Bellberry supports the use of novel trial designs seeking to improve the quality, efficiency and effectiveness of the drug development process.

Definitions

DSMB: Data Safety Monitoring Board
IB: Investigator's Brochure
MAD: Multiple Ascending Dose
MTD: Maximum Tolerated Dose
PD: Pharmacodynamics

PICF: Participant Information and Consent Form
PK: Pharmacokinetics
SAD: Single Ascending Dose

SAD-MAD Study Designs

The aims of a SAD study are to assess the tolerability, safety, pharmacokinetics (PK) and can incorporate, the pharmacodynamic (PD) effects of a single dose of the investigational drug.

The aims of a MAD study are to assess the tolerability, safety, PK and, if possible, the PD effects of repeated (multiple) doses of the investigational drug. Like the SAD study design, MAD studies usually involve small cohorts of participants, with appropriate review of safety data for each cohort before escalating the dose in the following cohort. The starting dose may be the same as for the SAD study or could be based on the minimum anticipated efficacious dose (provided this is lower than the MTD established in the SAD study). A third option is to select a starting dose for the MAD study that is one or two dose levels below the MTD established in the SAD study. Sentinel participants are not usually included in MAD study designs. Like SAD studies, MAD studies may either be open-label, or include a small number of participants in each cohort who receive placebo formulation in randomised, double-blind fashion.

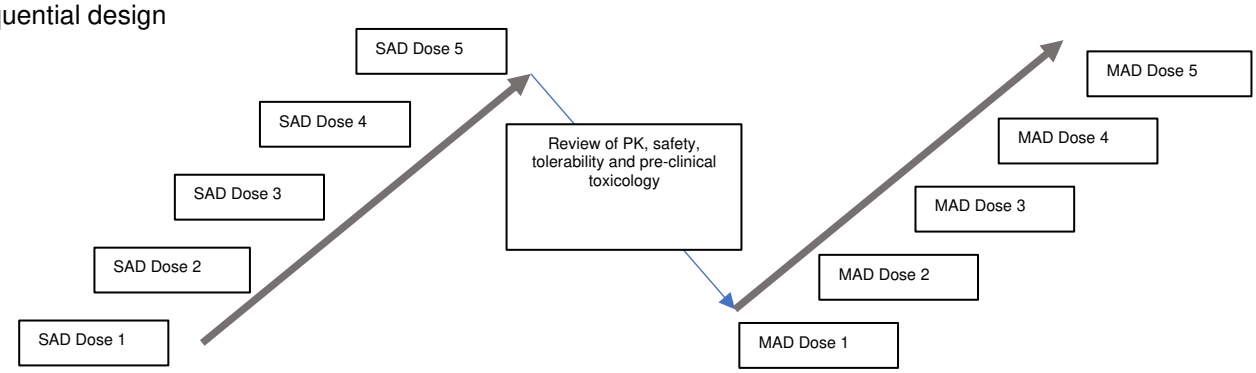
In the conventional combined SAD-MAD study design, the SAD portion is completed before the MAD part is initiated. Safety and PK data (and PD data if available) from all single-dose cohorts are reviewed to establish an appropriate starting dose for the MAD part of the combination study.

In recent years, various alternative study designs have been used to accelerate Phase 1 development of new medicines, and to enable earlier commencement of Phase 1b or Phase 2a studies in the target patient population. Umbrella protocols typically allow for multiple doses to be investigated before completion of the SAD component, as soon as sufficient data are available from the SAD phase to demonstrate safety of the starting dose in the MAD phase. They may also include investigation of food effect at a single dose level (again starting before completion of the SAD stage, assuming sufficient safety data are available from the SAD stage to support the selected dose). Other components may also be included, such as evaluation of PD biomarkers, PK-PD relationship, population differences (elderly, ethnic groups, gender differences), different drug formulations, and investigation of potential drug-drug interactions.

HREC approval of multi-stage phase 1 protocols in healthy volunteers

The following figures illustrate combined SAD/MAD study designs in comparison with conventional SAD/MAD designs:

Traditional or
Sequential design



Integrated/ov
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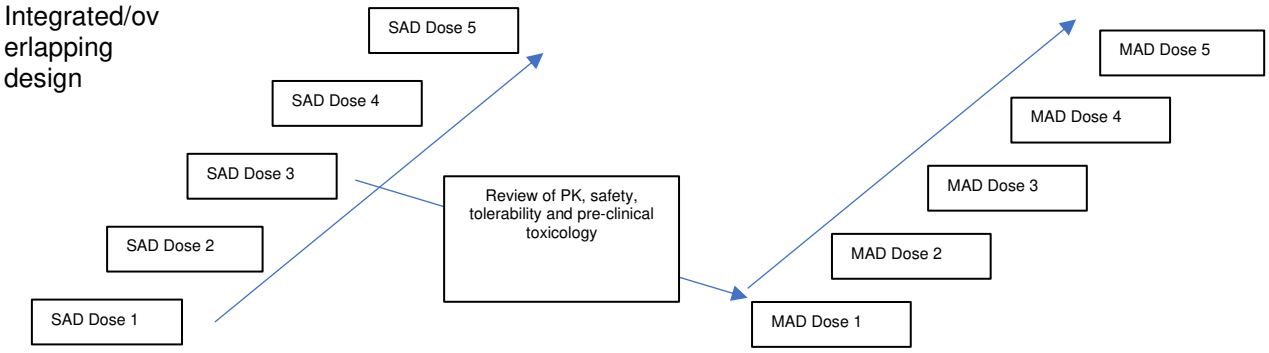
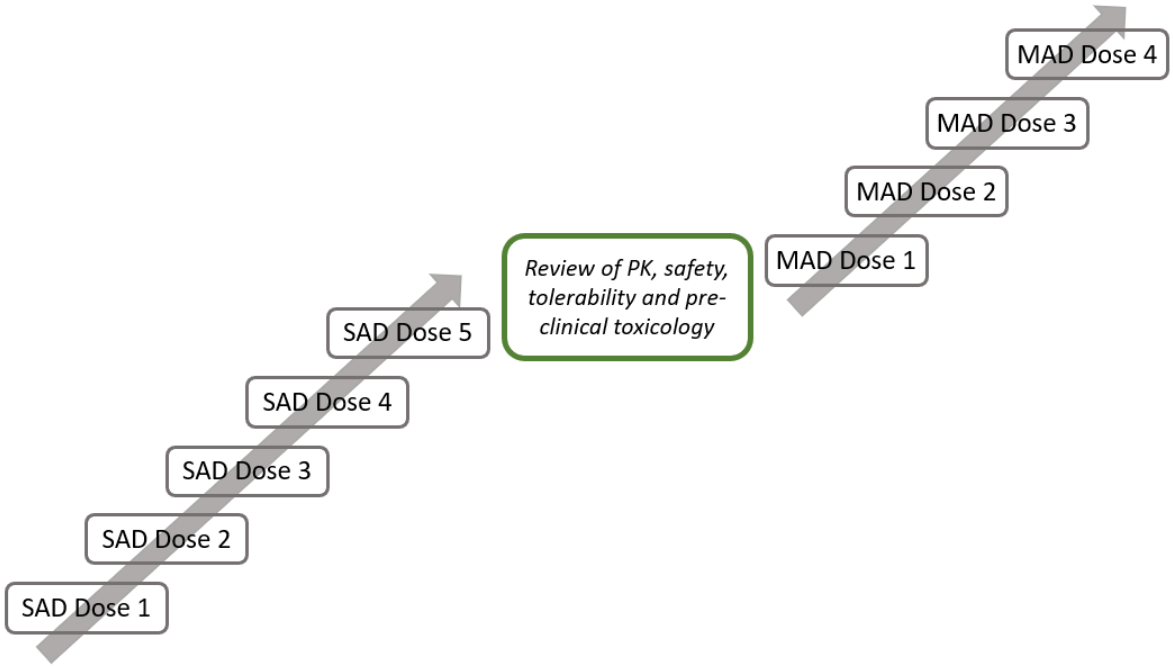
design





One of the objectives of a SAD investigation is to confirm

A major challenge in combined SAD-MAD protocols is the need to incorporate appropriate safety information from the initial SAD stage into the study documents, including the Participant Information and Consent Form (PICF) for subsequent stages.

For both the sequential and integrated study designs, any approval will be for Part A/Stage 1 only with approval for Part B/Stage 2 subject to satisfactory submission and approval of justification of the dose for Part B/Stage 2. Generally, an approval for a combined SAD MAD protocol will carry a condition requiring confirmation of DSMB approval to continue. This must be submitted for HREC review as an amendment along with any relevant updates to PICF and study documentation.

Progress to the MAD phase will be subject to the satisfactory submission and approval of a safety report and any relevant amendments to the PICF and study documents following the completion of Cohort X of the SAD phase (if required). This amendment is required to be submitted and approved prior to the commencement of Cohort 1 of the MAD phase.

The HREC must be also satisfied that adequate DSMB arrangements and stopping rules are in place. Therefore, if approved, a condition will be placed on the progress of the study. This condition will be outlined in the approval letter. The condition will confirm:

- The approval of the SAD stage of the study as applicable.
- The point at which further information is required before progressing to the MAD stage. This will generally be at the completion of the SAD stage for sequential studies, and at the nominated cohort point for the integrated design studies.
- Justification of the proposed starting dose and dosing intervals for the MAD stage. The arguments will be based on PK analysis and safety analysis from SAD cohorts and be supported by pre-clinical toxicology data. In general, there will be DSMB review of data from the first two or three cohorts at least.
- Amendments to the study related MAD information in the protocol/IB/PICF reflecting the updated information (if required).
- The revised PICF for the MAD stage should include information about the actual doses to be administered in the MAD stage (if these are dependent on the SAD results) and appropriate safety data from the SAD stage.

These updates will be required to be submitted as an Amendment for the HREC review. The HREC will consider whether:

- The starting dose for the MAD stage or other additional component is adequately supported by emerging data from the SAD study;
- The total dose to be administered in the subsequent study part is supported by the nonclinical toxicology data;
- The proposed dose interval in the MAD or food-effect component is adequately supported by PK data from animal studies and the ongoing SAD component so that the HREC can evaluate the potential for accumulation with multiple dosing;
- A summary of the available safety data from the completed SAD cohorts is submitted with and/or incorporated into the revised PICF for the subsequent component(s), as an application amendment.

If important safety data such as new dose-limiting toxicities emerge during the ongoing SAD stage, this information must be submitted to the HREC for review and should be incorporated into revised PICF documents for all study parts that are still in progress.