Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

KCE Sponsor budget tool guidelines

These guidelines refer to version 3.2 date 13/12/2018 of the KCE sponsor budget tool

The aim of the budget tool is twofold: first, to make sure the applicant considers all necessary trial activities for the budget; second, to facilitate a fair and similar compensation across the trials funded. It remains however a tool and individual trials may have specific budget needs that need discussion on a case by case base.

Although in the outline stage of a project, it might seem difficult to complete the budget tool (e.g. partners may not have been identified or quotes requested), we expect candidates to consider the different parameters and tasks in making a first draft budget. The initial budget will be considered 'draft' during the initial selection steps and will not be a selection criterion at this stage. This budget is still subject to change between the different steps of the review process (from outline to full research proposal to recommendation for funding and to final contract). The final budget will be the result of changes to the research proposal based on input from the Trials Board and budget negotiations with the KCE Trials Team and will need approval by the KCE Board.

The budget template consists of different tabs detailing the study parameters, budget parameters, the overall costs and the site costs. Extra tabs can be used if needed, for example to detail the costs of a contractor/collaborator. **The budget template is pre-filled with study related tasks but will need to be adapted according to each specific protocol.** Lines and tasks can be deleted or inserted as appropriate, however the general principles of the type of tasks allocated to a subheading should not be changed. For general tasks a fixed price (FX) has been determined; where relevant, formulas related to the study parameter have been inserted. Note that only in very rare cases for non-standard studies the fixed amount may be adapted by KCE after justification from the sponsor. If an update is needed to the standard formulae or fixed price, a comment should be included in the comments field (Column K) including a justification. This change is subject to review and prior agreement by KCE.

COLOR CODING

GREEN: DO NOT CHANGE

Cells in **green** contain formulas and are automatically calculated based on cells completed in other parts of the excel sheet. **You should not change a figure in green**. By adding information elsewhere e.g. in the study parameters tab, this figure will be updated automatically.

YELLOW: YOU NEED TO COMPLETE

Cells in yellow need to be completed to allow for automatic calculations throughout the worksheet.

This guideline document gives instructions on each of the tabs. Additional information is provided in the 'how to complete' tab of the budget tool excel file.

For international studies when the sponsor is outside of Belgium: a specific budget tool, only taking into account the tasks of a Belgian Coordinating Centre and accompanying guidelines have been developed and should be used to calculate these budgets.

For international studies when the sponsor is in Belgium: The budget tool should clearly mention which proportion of all study patients are planned to be included in Belgium. A document detailing the delegation of responsibilities and funding from other funding bodies should accompany the budget table.

The budget tool and guidelines are developed by KCE Trials. If you wish to use this budget tool outside the KCE Trials Programme, you should contact trials@kce.fgov.be.

Tell us how and why you wish to use the tool. Please include your contact details: name, institution/company, address, telephone number, and email.

STUDY PARAMETERS

In this tab, the general information about the trial and the trial timelines should be provided. Some of the information in the cells will be automatically transferred to the other worksheets. Do not insert or delete lines in this tab as the links to the overall costs might no longer work. In case your project would require additional lines, please contact KCE Trials to discuss. This can be the case when your project has a long follow-up period or has seasonal recruitment periods during which more or less intensive activities are needed.

- KCE Reference: the KCE Reference number is assigned when the project is recommended for funding by the Trials Board and can be found in the Trials Board decision letter, e.g. KCE-18001.
- Planned number of subjects (screened, randomised, completed)
  A screened patient means a patient that has signed informed consent and was formally asked to participate in the trial. As pragmatic trials have only a limited number of inclusion/exclusion criteria, the number of patients screened is not expected to differ much from the number of patients randomised.
  In exceptional circumstances, where a high drop-out rate during the study can be expected, the number of patients completed might have an impact on the budget. In that case this should be reflected in the tab site visit costs. E.g. if a high drop out rate is expected, only a % of patients will perform all visits (less monitoring, medication, … required for the follow-up part)
- Number of protocol related visits per subject = the number of visits where data collection will be performed including the standard of care visits
- Number of sites
- Study timelines
  - FPI: First Patient In (first patient signed informed consent)
  - LPI: Last Patient In
  - LPLV: Last patient Last Visit
  - DBL: Database Lock
  - CSR: Clinical Study Report
- Note that the time between LPLV and CSR should not exceed 6 months
- The on-site and off-site monitoring frequency (if relevant) needs to be determined as well as the number of CRAs on the project (take into account back-up CRA, note that having 2 CRAs does not necessarily mean 2 FTEs) – the monitoring frequency should be defined after a thorough risk-assessment of the trial and should be justified in a monitoring plan. More information can be found in section 3 Monitoring.
  KCE expects that as a minimum quality check, all Informed Consent forms and patient existence will be verified in all participating sites. Regarding the primary variable as far as not reported by the patients themselves, source data verification should be done according to the instructions in the monitoring plan.
- Expected number of reportable SAEs
  Note that this is a pragmatic trial, the expected number of reportable SAEs should be based on the safety reporting requirements in the protocol (which are in turn based on the risk assessment). Further details can be found in section 6 Safety

The timelines for the study start at the milestone "first patient in". Time that is invested in tasks before that date are included in fixed prices. The sponsor can ask for an advance payment (max € 12 500) to help support the development of the protocol if a proposal is shortlisted and invited to submit a full research proposal (FRP). As soon as there is a recommendation to fund, a second advance payment (max € 12 500) can be requested to support the study set-up and the feasibility. These upfront payments are part of the budget, however if the study would not receive final endorsement by the KCE Board, the advance payments do not need to be refunded by the applicant.

Trial timelines should be estimated for the analysis and reporting of the primary endpoint. In cases where the data collection time points for secondary endpoints deviates considerably (e.g. 12 months or more) from the primary endpoint, a separate budget should be developed and included as an additional excel sheet/tab in the file. It should reflect the less intense follow-up for the periods and tasks involved in this long-term follow-up for secondary endpoints.

BUDGET PARAMETERS

In this tab the standard hourly rates/fees for the different roles involved in the study are mentioned. These rates are largely based on KCE report 178 https://kce.fgov.be/publication/report/manual-for-cost-based-pricing-of-hospital-interventions that analysed the cost of personnel working in hospitals. Based on a yearly number of hours of 1976 and taking into account paid holidays (24 days), public holidays (10 days), education and training (3 days), sick and accident leave (7 days) and other absences (5 days) the number of productive hours is estimated at 1605.2 hours. The rates have been adjusted for indexation and include the 2017 indexation. The rate for the CRA has been adjusted to include transportation. KCE recommends that you use these rates to build your budget. Exceptions are possible in very specific circumstances, but should be justified by information from the university/hospital HR department and are subject to review and prior agreement by KCE. In case an individual rate is higher because of seniority, KCE considers this will be counterbalanced by the margin as well as lower individual rates for other roles.

The aim is that the estimation of the number of hours per activity by the sponsor and the sites should be as accurate as possible (not underestimated nor overestimated). In addition, KCE has added a margin of 15% to account for future indexation, unforeseen delays and extra costs or capacity needs during the study. This is to support the learning curve in the first years of the KCE Trials programme. Note that for items with a fixed cost no margin should be added.

OVERHEAD

KCE accepts a maximum rate of 17% for overhead costs.

Adding full overhead costs for expensive fixed cost items (> €10.000) may not be appropriate and will require discussion on a case by case basis.

There is no overhead for the sponsor on the site costs, however overhead costs charged by sites with a maximum of 17%, can be included.

The start-up costs for the site are set at €1000. This amount will be lower if working with GP sites (suggested fee of 250€) and can be higher if working in a complex setting involving several departments, pharmacy, lab etc. It should cover the costs for the site involved in the preparation for the initiation of the study (contracts, training, site set-up).
There is a fixed amount set, to cover the costs of the transportation for the monitoring visits, a margin is included, overhead does not apply.

OVERALL COST

General Guidelines

The number of suggested hours for each task are real life estimates and should be sufficient to cover the task. Several factors such as the complexity of the trial, the location and organisation of the participating sites (e.g. GPs, hospitals, presence of trial nurse, …) will drive the cost. A 'reality check' of the total amount of each section is part of the budget building exercise.

It is not the intention that the maximum suggested number of hours is used as a general rule. Sponsor-CI teams will have to justify the time they think is needed.

KCE has populated the grid with roles (team member column) that are relevant to the performance of each defined task. This allocation is not mandatory to follow and can be changed according to the organisational structure or the type of trial. However the tasks undertaken by a role should be appropriate for that role e.g. a Chief Investigator should delegate all activities that can reasonably be delegated to people with the necessary profile, experience and qualifications e.g. a junior PhD student should not be given the role of Project Manager for a multicentre RCT and vice versa a senior Project Manager should not be doing tasks that can be done by an administrative assistant.

FIXED AMOUNTS

For several tasks, a fixed amount (FX) has been calculated that represents the total of the time invested by the different roles. E.g. Project design and set-up include protocol development where the Chief Investigator, Project Manager, Statistician and Health Economist are all involved. The total estimate of the time and costs related to this have been integrated into a fixed amount. (FX in the team member columns)

Depending on the study setting (e.g. hospital based, GP practices, specialist centres) the time needed may vary. The grid has been developed for a low/medium complexity (based on data points and safety) trial in a hospital setting.

1. Project Design and Set up

This section includes all activities that are performed to enable the set-up of the project and that are required before the project undergoes regulatory/ethics review. There are two parts in this section: one fixed and one variable, based on number of sites to be visited.

Section 1a FIXED AMOUNT

This fixed amount includes the following:

- Development of the protocol (including patient and public involvement, statistics, health economics, internal and external review, …); in case experts are consulted, the cost for travel, etc should be covered by this amount.

- Development of patient related documents (e.g. Patient Information Sheet and Consent Form, specific questionnaires, …) including any translations
- Development of agreements with funder, vendor/contractors. KCE has templates that can be used for this purpose.
- Costs for review of documents related to this section
- Initial selection of participating sites/GPs

The feasibility of the study depends on the number of sites and their experience in setting up and running randomised clinical trials. In the current pre-populated grid, 50% of the sites are scheduled to have an on-site feasibility visit and 50% of sites are scheduled to have a remote feasibility visit.
For large scale trials (e.g. more than 30 sites), KCE suggests an on site visit in 10% of the sites and remote feasibility check in the remaining 90% of the sites.
A minimum of 3 to 4 on site feasibility visits may however be needed, especially if the type of research is new for the site.
The conduct of the feasibility and site selection visits is the responsibility of the sponsor. In addition, KCE Trials will ask a contract research organisation (CRO) to complete an additional check of recruitment feasibility. Where appropriate, the sponsor feasibility visit and the CRO visit to the site can be combined.

The set-up, negotiation and finalisation of agreements with sites will depend on the number of sites involved. KCE templates are strongly encouraged to be used, as they are back to back with the sponsor-KCE agreement.

In case GPs are involved or in situations where there is no negotiation with hospital direction required, the fixed amount for the contract development and negotiation needs to be reduced. The set-up, negotiation and finalisation of agreements with external collaborators can be added here (you will need to adapt the formula as it only takes into account the number of sites). The fee for contracts with external collaborators is to be reduced to 500€ per contract in case no public tender is needed.

License fees for the use of questionnaires are to be included in this section however if an app, IT platform or another tool is developed, the costs for this should be detailed in section 13a, study specific equipment unless they are integrated in the eCRF platform. Note that if the intervention itself includes an app or software that requires development, these development costs of an app or software cannot be part of the trial budget.

2. Regulatory and Ethics Review

This section should include all costs that are related to:

- Development of medicinal product/device related documentation including IMP label related activities (design, translation), if applicable and if needed for regulatory/ethics review
- The logistic activities for the submission of the dossier to the Ethics Committee(s)
- The logistic activities for the submission of the dossier to Competent Authorities, if applicable
- Provision of insurance, according to the legislation

As soon as the EU Regulation is implemented, this section will need to be adapted. Please contact KCE Trials if this is the case for your trial.

3. Monitoring

The purpose of trial monitoring is to verify that

- The rights and well-being of human subjects are protected
- The reported trial data are accurate, complete, and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirements

Source: ICH-GCP E6 (R2) 5.18

This section should include the cost for the monitoring of the trial as specified above and should take into account a risk based approach. The monitoring of a low-risk, pragmatic trial will require less frequent on-site monitoring visits and can even be done completely centralised. It is important to develop a monitoring plan as soon as possible to determine the monitoring requirements and frequencies for the specific trial.

There is a fixed amount foreseen for the transportation costs of the monitors.

The development of a monitoring plan (fixed amount) and all costs related to the implementation and follow-up of the study at the participating sites are to be covered in this section:

- **Pre-study visit** (if applicable e.g. in case not all questions were covered during the feasibility or the feasibility was done remotely)
- **Training of CRAs**: this is the time needed for the CRAs to study the protocol and to get familiar with the disease area. It is not the training that is delivered to the sites (this is included in initiation visit and investigator meeting)
- **Conduct of initiation visits**. The suggested time (16 hours) needs to be adapted in case of remote initiation, investigator meetings counting as initiation visit or blended formula. Also the complexity of the trial and the involvement of different departments will need to be taken into account; e.g. time needed for an initiation visited at a GP practice will be considerably lower than a trial which involves different hospital departments, pharmacy, lab etc. The suggested standard time for studies with GPs is 8 hours. The formula can be adapted as such and a comment should be added in the comments field (column K). The suggested time includes the time to prepare, conduct and follow-up the visit and also includes the travel time to the site as well as the cost for travelling.
- **Conduct of on-site monitoring visits**: The suggested time (16 hours) needs to be adapted for studies with GPs (suggested time for studies with GPs is 8 hours). The suggested time includes the time to prepare, conduct and follow-up the visit and also includes the travel time to the site as well as the cost for travelling.
- **Conduct of study closure**: The suggested time (16 hours) needs to be adapted for studies with GP's (suggested time for studies with GP's is 8 hours). The suggested time includes the time to prepare, conduct and follow-up the visit and also includes the travel time to the site as well as the cost for travelling.
- **Any remote monitoring activities**: for this activity, the formula contains 4 hours per contact per site but the time will highly depend on risk assessment, number of patients, number of data points. The formula should be adapted depending on monitoring plan and a comment should be added in the comments field to justify the change.– This activity can be split between data manager or CRA.

The time allocated to each activity in this section is for a study of medium complexity. It should be adapted for studies of low complexity and should be justified in a monitoring plan.

4. Quality Assurance

Section 4 FIXED AMOUNT

This fixed amount has been calculated for a 2 day sponsor audit and 2 day visit on site including preparation, reporting and follow-up.

This activity should be taken care of by an independent quality department. It can be the quality department of the hospital or can be outsourced. The cost for the outsourcing of this activity should be covered by the amount in this section.

5. TMF Handling & Administration

- This section includes all administrative activities related to the documentation, collection and archiving of essential documents: set-up and maintenance of a (e)TMF, (e)ISF, set-up and maintenance of a study portal.
- A fixed amount has been calculated for the general set-up.
- All activities that are dependent on the number of sites involved, are mentioned on separate lines.
- If extra budget is needed for shipments of study material (e.g. in case of a fully remote study initiation) this should be included on a line 5c "Shipment and Distribution Services".
- This section includes the administrative work involved in the set-up, execution and follow-up of invoices and payments by the sponsor. Prior to the invitation to invoice, the amounts should be confirmed by data manager, CRA and project manager.
  This needs to be adapted according to the agreed number of payments and depending on the trial setting (could be once yearly); if KCE is responsible for site payments, line 5f should be deleted.
- Archiving: fixed amount of €250 per large box, assuming 2 boxes for the whole trial and 1 box for every 4 sites for 25 yrs archiving.

6. Safety

This section includes all activities related to the evaluation of the safety of the intervention studied (IMP, device, procedure, …).

The number of reportable SAEs should be estimated in the tab study parameters. Note that this should only cover the SAEs that require reporting (SUSARs) or expedited reporting, as defined in the protocol. As the majority of trials within the Trials programme are pragmatic trials with registered medications used within the label, the expected number of reportable SAEs will be low.

For studies not involving IMP or devices, the safety evaluation and follow-up will be based on the risk assessment as documented in the protocol. This section might be not applicable in certain study settings.

Section 6 FIXED AMOUNT:

This fixed amount includes:

- Follow-up of reportable SAEs (SUSARs or SAEs as specified in the protocol)
- Writing of SUSARs (if IMP)
- Reporting to EudraVigilance Database (if IMP) materiovigilance reporting if device
- Meetings on safety findings with DSMB (if IMP, can be Steering Committee otherwise)
- Reconciliation of the safety database

Note that if safety management is outsourced, overhead does not apply.

7. Data Management

This section includes all activities related to the data management activities for the clinical trial. Keep in mind that the number of data items collected should be kept to a strict minimum and should only address the research questions in the protocol. All data collected should be analysed.

In case the study runs over a long time (>4 years), additional budget might be required for data management activities.

Section 7 FIXED AMOUNT

This fixed amount includes the following:

- Design of eCRF
- Design of Clinical Trial Database and Safety database if applicable
- Writing of the Data Management Plan
- Data Coding of adverse events (if applicable)
- Data Coding of medication (if applicable)
- Programming of queries to be sent in batch
- Running query batches and distribution to sites.
- Follow-up on query resolution
- Import of data (ECG, lab, images, … if applicable)
- Database lock

The fixed amount proposed makes a distinction between a trial of low complexity and a trial with moderate complexity. The distinction between low and moderate complexity should be based on the number of data points and the required safety follow-up. Repurposing trials would typically qualify as a moderate complexity trial, whereas a comparative effectiveness trial would typically be a low complexity trial. This should be justified by the sponsor and agreed upon by KCE.

Note that in case data management is outsourced, overhead does not apply.

8. Statistics, report and publication

This section includes the activities related to the statistical analysis for this trial, from statistical programming to collaboration between statisticians and clinical team to write the clinical study report.
Statistical input at the study set-up (including activities related to the randomisation process) is already budgeted under section 1.

Section 8 FIXED AMOUNT

This fixed amount includes the following:

- Statistical programming
- Generation of tables and listings
- Development of a Statistical Analysis Plan
- Statistical analysis and reports
- Generation of the Clinical Study Report, including meetings and review
- Writing and submission of the publication
- Any costs to ensure open access to the main publication of the study

Note that if statistics is outsourced, overhead does not apply.

Note that:

- Subsequent publications should not be included in the budget
- Any investigator meetings planned to present the trial results should be included under section 9 Project Management
- Regarding the health economic analysis, the study budget will include costs of collecting data required to perform the health economics analysis (e.g. EQ5D) however the costs of performing the actual analysis will not be budgeted. Depending on the study results a health economic analysis may be justified. This will be a separate project and the options are listed elsewhere (LINK). Involvement of a health economist in the development of the protocol, is covered in section 1.

9. Project Management

This section consists of the project management activities that are not mentioned in any of the above sections. It takes into account time needed for the generation of study specific documents (communication plan, development of newsletters, …), the day to day follow-up of the trial (contact with key stakeholders, planning of meetings, follow-up of recruitment, follow-up of budget …). Costs related to activities detailed in the other sections above need to be included in their respective sections rather than attributing them to the role of PM in this section (e.g. development of regulatory documents need to be included in section 1 or section 2).

- Project Management, other
    - As an example, time needed for day to day follow-up for a study with 10 sites and 100 patients in continuous follow-up for 1 year is estimated as 0,5 FTE. This example can't be considered as applicable to every trial and needs to be adapted (but not multiplied) in case of more/less sites or patients.
    - Include the motivation for the time estimated for project management according to the setting of your study.
- Project Status Reports (update KCE), during the recruitment phase of the study, regular updates (2-weekly) are required. An additional line will capture the less frequent reporting (monthly) after the recruitment period
- Investigator Meeting(s)
- Steering Committee Meeting(s): time and travel for external attendees should be covered by the fixed amount. The frequency is set at 3 meetings/yr for the first year, followed by 2-yearly meetings for the consecutive years.
- Study team meetings are budgeted with a fixed amount per meeting taking into account the presence of the majority of the Study Team/Trial Management Group. The frequency is estimated to be 2-weekly during the recruitment phase, followed by monthly meetings during the follow-up phase of the study

10. Patient and Public Involvement

This section includes the costs related to the involvement of patients or patient representatives in the trial. KCE expects that patients will be consulted and involved before the endpoints are defined and the study outline is submitted under the KCE Trials programme. In addition to their input on the choice of patient important outcomes, patients should evaluate the burden for the patient of participating to the trial, review of patient information and consent form, …

Section 10 FIXED AMOUNT

The fixed amount in the budget tool takes into account the financial support for 2 patients or patient representatives including transport, preparation and attendance to meetings.

A separate line has been included to cover the costs for attendance to TSC.
If specific activities for patients will be organised, this can be included on a separate line.

11. IMP/Intervention Handling

In case the study requires a specific Investigational Medicinal Product, a device or a special intervention, all costs for purchasing, labelling, developing, tracking, etc. need to be included here. As KCE trials are pragmatic trials, efforts should be made to prescribe and invoice medication or other interventions as in routine practice. The KCE Trials programme is considered as a pilot programme for pragmatic trials by the Belgian regulatory authorities and may be able to negotiate trial specific reimbursement conditions in Belgium.

- Sourcing of IMP, comparator/placebo, device, … (including import license if applicable)
- IMP or intervention accountability, will vary for pragmatic trials
- Randomisation related activities (Codes, IXRS,…) if not taken care of by the eCRF system
- Packaging, blinding, labelling
- Storage, distribution, maintenance
- IMP destruction & recovery unused products

This section is not pre-filled as it will highly depend on the type of IMP/device/intervention.
In case IMP handling is totally outsourced it should still be captured in this section. Provide quotes regarding the costs for outsourcing to document the costs in this section.
In general, no overhead can be applied on these costs.

12. Overview of Site Costs

To report site costs, you have 2 possibilities

1/ Report site costs in the overall costs (line….) – with an automated formulae (2 hours per visit for study nurse and 10 minutes per visit for PI). The automatic calculation in this section takes into account an average estimated time required by the study nurse and local investigator for the administration and follow-up of a pragmatic clinical trial which should be as close to Standard of Care as possible.

Or

2/ Report site costs in the separate tab and include all procedures per protocol (see below)

In case the study requires non-standard of care visits and/or procedure/investigations, it is advised to detail the site costs in the separate tab detailing the costs according to the activities required by the protocol. Start-up costs for sites are taken from the budget parameters tab.
The overhead and margin can be added to site costs and should be paid to the sites.

A separate line in foreseen to cover the time for the use of EDGE, a web-based software tool in order to allow each participating site and KCE to monitor the recruitment at the participating sites in an anonymized manner "in real time". KCE will provide the tool free of charge. In an effort to stimulate the uptake of this new tool,

a flat fee of €25 (excl VAT but including margin and overhead) per patient is budgeted for the recording of enrolment, randomization and completion in the EDGE tool within 5 working days of the respective visit. This is budgeted on top of the normal patient fee.

If the costs are detailed in the separate tab 'site costs', the automatic calculation in the tab 'overall costs' should be deleted. Otherwise, site costs are counted twice.

13. External vendors/contractors and central review

All costs related to the outsourcing of activities that do not relate to any of the above (e.g. central review, …) should be included in this section.
This section should also include costs for any specific equipment that needs to be purchased for the study.
It should not include material needed for the day to day business of the personnel working on this study (e.g. PC, printing, paper, …)
It is highly recommended to provide supporting information such as quotes (preferably from different providers) to support the amounts in this section. Candidate sponsors should check institutional procedures and regulatory requirements related to the need for (public) tendering.
In general, no overhead or margin can be applied on these costs.

🗀 SITE COSTS (details)

In this tab an overview of protocol specific tasks should be generated. All activities that are considered as Standard of Care cannot be charged to the study budget. As KCE trials are pragmatic trials, the data collected should come from routine medical data. However study specific costs (Informed Consent discussion, investigations, pharmacy, …) and time spent for the administration and data entry can be included here.

If you have any questions please don't hesitate to contact Trials@kce.fgov.be