



## USER INSTRUCTIONS FOR THE RISK-BASED MONITORING SCORE CALCULATOR

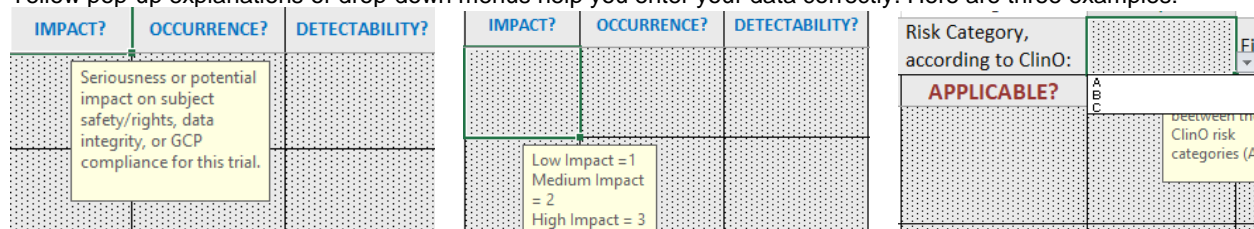
### General instructions

This **Risk-Based Monitoring (RBM) Score Calculator** was developed by the Monitoring Platform of the Swiss Clinical Trial Organisation (SCTO) and first released in June 2019. These user instructions enable you to calculate and determine the recommended monitoring strategy for a particular clinical trial you are planning, by completing a spreadsheet-based questionnaire. Once you have completed the information related to each risk score, the RBM Score Calculator provides you with an overall answer. Your user feedback is welcome to help us to improve our calculator.

These instructions refer to the related protected Excel sheet of the RMB Score Calculator, itself (hosted at [www.scto.ch/monitoring](http://www.scto.ch/monitoring)), meaning that you can only work in and fill out stippled grey cells: . Other cells, primarily providing supporting information or explanations, are legible but locked.

For each data field you need to complete, a pop-up box containing help text prompt indicates the format to be used, e.g. for a date, the pop-up indicates: **dd.mm.yyyy**. Note that column J (Comments/Rationale for the Risk Factor) does not supply prompts, however, as it is for you to make your own notes in.

Yellow pop-up explanations or drop-down menus help you enter your data correctly. Here are three examples:



The calculator lists **23 Risk Factors (RF)**, classified in seven categories. For each RF, a description and some questions to consider are provided for you in column D.

To start, for each RF, you need to determine and enter the applicability in column E. If a RF is not applicable to your study, the other columns to the right can be left empty.

If a RF is applicable, in columns F (impact), G (occurrence), and H (detectability), you should enter a score of 1, 2, or 3: indicating low, medium, or high **impact**; low, medium, or high likelihood of **occurrence**; and easy, moderately easy, or difficult **detectability**, respectively.

**Impact** is defined as the seriousness or potential impact on subjects' safety and rights, data integrity, or Good Clinical Practice (GCP) compliance; **occurrence** is the frequency of the RF; and **detectability** is the ease with which the risk can be detected by the monitor. Explanations and examples to help you score impact, occurrence, and detectability for each RF are provided below.

For each RF, the **risk score** in column I is then automatically calculated by multiplying the three scores provided – for impact, occurrence, and detectability. Note that if you fill out columns F to H for a RF, but set the RF to “not applicable” in column E, the risk score calculation will nevertheless be 0.

A RF of 1–3 is considered low, 4–9 as medium, and 10–27 as high.

Total numbers of low-, medium-, and high-RF are then automatically calculated and will appear in cells I26–28. The recommended monitoring strategy for your study is automatically calculated in cell I29, once you have entered the study risk category according to the *Ordinance on Clinical Trials in Human Research* (ClinO) in cell F1.

## First row: identifying your information

Enter the study title or acronym (or code, if it should remain confidential), the study risk category according to ClinO (A, B, or C, in the drop-down menu), the identity of the person filling out the calculator, and the date.

## Risk factors

The colours used below for the seven categories of the 23 RFs correspond to those in the RBM Score Calculator itself.

### I. Subject

#### 1. Vulnerable population

These subjects may include children or teenagers, healthy volunteers, students, pregnant women, geriatric subjects (over 80 years), those with cognitive or psychological disorders, immigrants, prisoners, etc.

- Impact: this depends on the study and type of vulnerable persons. E.g. a study with electronic questionnaires could be highly affected if the population is geriatric and is not familiar with using electronic devices (score = 3).
- Occurrence: e.g. if the study population is constituted of half adults and half children, the occurrence should be score = 2 (medium).
- Detectability: this should be quite easy to detect, as the monitor has full access to the Informed Consent Form (ICF), (score = 1).

#### 2. Emergency situation

Consider if problems may occur with informed consent, assessment of eligibility criteria, immediate trial-related processes (such as diagnosis and therapy). “Emergency” is defined as necessity of immediate start of therapy (<12h), irrespective of the severity of the disorder.

- Impact: this depends on the study design.
- Occurrence: e.g. if 100% of the study subjects are enrolled in emergency settings, the occurrence should be score = 3 (high).
- Detectability: this should be fairly easy to detect as the monitor has full access to the ICF (score = 1).

#### 3. Complexity of consent process

Consider if there are multiple ICFs (such as pre-screening or sub-studies).

- Impact: e.g. if a pre-screening consent is necessary, the impact should be score = 3 (high).
- Occurrence: e.g. if 100% of the study subjects are supposed to be enrolled in sub-studies, the occurrence should be score = 3 (high).
- Detectability: this should be fairly easy to detect, as the monitor has full access to the ICF (score = 1).

### II. Design

#### 4. Complexity of eligibility criteria

Consider the number of criteria, ability to verify them, critical criteria (safety-relevant, relevant for the effectiveness of the therapy, relevant for the validity of the results), population stratification, documentation required for diagnosis, central vs. local laboratory, timelines of assessment, special tests/assessments for eligibility evaluation not routinely performed, etc.

- Impact: the more the eligibility criterion is related to the endpoint or subject’s safety/rights, the higher the score should be.
- Occurrence: this depends on the number of complex criteria.
- Detectability: e.g. if the criterion concerns a medication taken by the subject over the past 20 years, then score = 3; if the medication was taken in the past 2 days, then score = 1 (easy to detect).

Swiss Clinical Trial Organisation

**User Instructions for the Risk-Based Monitoring Score Calculator**, first released June 2019

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## 5. Complexity of design

Consider number of arms, adaptive design, randomisation, number of visits, dose, complicated or unusual procedures, study duration, strict timing for certain procedures, number of sites or centres, etc. Is it likely that the subject/investigator will not adhere to the treatment schedule?

- Impact: e.g. a study with an adaptive design should have a high impact on the subject's safety (score = 3).
- Occurrence: e.g. in a study with two groups, one with a simple design, and the other with a complex design, score = 2 (medium).
- Detectability: e.g. in a dose escalation design, this RF should be easy to detect (score = 1).

## 6. Complexity of primary endpoint

Consider the robustness of the endpoint (objective/subjective, soft), if its assessment is complex or not standard (e.g. composite endpoint), and if special requirements are needed for its assessment.

- Impact: this should often be score = 3.
- Occurrence: this should often be score = 3.
- Detectability: e.g. a composite primary endpoint should be score = 3, since each of its components could constitute a source of error. A primary endpoint obtained by imaging measurements should be score = 3, if special skills are required to verify it.

## 7. Bias impacting the primary endpoint

Consider if there are any sources of bias or variance with regard to the endpoints. This can happen, for instance, if the trial is not randomised or is open label.

- Impact: this depends on the design, e.g. for an unblinded study, in which the primary endpoint is the Physician Global Assessment (PGA), impact should be score = 3.
- Occurrence: if bias is supposed to occur in 100% of the cases, this should be score = 3.
- Detectability: this depends on the bias.

## 8. Additional treatment for concomitant diseases/symptoms

Consider if the study population is likely to receive additional treatment for concomitant diseases (with input from a medical doctor required), and if this could affect the (efficacy) endpoints.

- Impact: this depends on the study, e.g. if the endpoint is pain level in a population with chronic pain conditions, additional treatment could have a strong impact on the quality of data (score = 3).
- Occurrence: e.g. if 100% of the subjects are supposed to receive additional treatment, then score = 3.
- Detectability: e.g. if the subjects use a lot of over-the-counter medications, this will be difficult to detect for the monitor (score = 3).

## 9. Complexity of procedures

Consider unusual procedures.

- Impact: e.g. if the study implies a large number of visits lasting long hours with unusual procedures, this could burden the subject's participation and the impact should be high (score = 3).
- Occurrence: this should often be score = 3.
- Detectability: this depends on the study.

## 10. Withdrawal/drop-outs

Is there an increased risk of withdrawal or drop-out? E.g. might subjects withdraw from therapy or follow-up, as a result of very positive (or negative) therapeutic effects? Consider the possibility of noncompliance or withdrawal of consent. How is this taken into account in the trial design? In trials focusing on efficacy differences, drop-outs could bias the results. Consider subject compliance in case of self-treatment administration.

- Impact: e.g. score = 3 if the study design could encourage a large number of withdrawal/drop-outs, except if their number is already included in the sample size calculation and is realistic, or if it is planned to replace withdrawal/drop-outs (then score = 1).
- Occurrence: make an estimate.
- Detectability: this should often be score = 1.

### III. Safety

#### 11. Serious drug reaction/device effect

Consider if the trial therapeutic intervention is known to have any serious drug reaction/device effect. Have any events of special interest been identified? Consider any protocol-specific reporting requirements for Serious Adverse Events (SAEs).

- Impact: e.g. this should be low (score = 1), if the Investigational Medical Product (IMP) is a marketed drug with a well-known safety profile.
- Occurrence: make an estimate, according to actual knowledge.
- Detectability: the score will depend on the depth of documentation of Adverse Events (AEs) in health data records.

#### 12. Interactions

Consider if there is a lack of previous experience on combination of trial therapeutic intervention being studied and other intervention/medications/devices. Pay particular attention to any basic or background therapies, prescribed, recommended, or allowed by the protocol, and to the timescale of potential interactions (see [www.epocrates.com](http://www.epocrates.com)).

- Impact: e.g. a study with two combined chemotherapies will have a higher impact on the subject's safety.
- Occurrence: make an estimate, according to the pharmacokinetic profile of the IMP.
- Detectability: this depends on the documentation of concomitant treatments in health data records.

#### 13. Subject population's conditions

Consider if the subject population's condition is critically severe: potential for SAEs/subject risk, or complexity of disease state. Consider high WHO/ECOG scores (in oncological subjects).

- Impact: this depends on the study.
- Occurrence: the score should be high if the population is constituted of subjects with multiple ongoing diseases.
- Detectability: this depends on the documentation of medical histories in health data records.

### IV. Intervention (IMP, IMD, surgery, etc.)

#### 14. Actual knowledge

Consider if there is only very limited knowledge about at least one of the trial therapeutic interventions: experience of the sites, special logistic requirements, product stability and expiry dates, likelihood of serious drug reaction/device effect, relative to standard medical care.

- Impact: e.g. a first-in-human study should be score = 3.
- Occurrence: e.g. in a study with two groups, one receiving the IMP, the other receiving a placebo, score = 2 (medium).
- Detectability: this depends on the intervention.

#### 15. Administration

Consider if IMP administration or MD utilisation is unusual, complex, etc.

- Impact: e.g. in a study with a chemotherapy administered intraperitoneally, while usually administered intravenously, score = 3.
- Occurrence: It should often be score = 3.
- Detectability: this depends on the intervention.

#### 16. Logistics

Are there any essential/unusual storage, preparation, or destruction requirements for the IMP or Investigational Medical Device (IMD)? It is necessary to analyse whether non-compliance with the storage requirements will actually increase the risk. Are there other trials using the same IMP/IMD (and, if so, evaluate the risk of confusion)?

- Impact: e.g. a study with IMP storage at 2 to -8°C should at least be score = 2.
- Occurrence: this should often be score = 3.
- Detectability: this should be quite easy to detect (score = 1).

### 17. Accidental or deliberate unblinding:

E.g. by obtaining laboratory values from a local laboratory, physical differences between placebo and verum, adverse events, unblinding of a subject for treatment decision after trial treatment, etc.

- Impact: e.g. in a study testing placebo versus an IMP with frequent Adverse Drug Reactions (ADRs), the score should be = 3 (high).
- Occurrence: this should often be score = 3.
- Detectability: this depends on the study design.

## V. Management

### 18. Sites

Are there enough staff? Qualified staff? Consider if the site or Principal Investigator (PI) is aware of their responsibilities (coordination/clarification of all issues/matters between the PI's unit and other units at their hospital e.g. radiology department, laboratory, etc.).

- Impact: e.g. in a monocentric study with a non-experienced site, score = 3.
- Occurrence: the overall participation is evaluated here (0–20 % of all sites evaluated as problematic = low occurrence (score = 1); 21–40% of all sites evaluated as problematic = medium occurrence (score = 2); 41–100% of all sites evaluated as problematic = high occurrence, score = 3).
- Detectability: this can be easily detected by checking training logs, etc., then score = 1.

### 19. Technical requirements

Consider if there are any technical requirements for the trial sites, e.g. access to diagnostic equipment, emergency equipment, unusual assessments to be done locally, new assessment tools, any essential processing, transport and/or storage requirements for material samples (e.g. biological samples, bio-banking which would require a fridge, freezer, a -80°C freezer, centrifuges, etc.) Consider to what extent the incorrect handling of samples may be critical.

- Impact: e.g. in a study sharing a hyperbaric chamber with clinical use, the impact should be high (score = 3).
- Occurrence: this depends on the study design/intervention.
- Detectability: this depends on the study design/intervention.

### 20. Staff requirements

Consider if there are any essential personnel requirements for the trial sites, e.g. trial-specific knowledge or training certificates, training requirements for assessment of the primary endpoint, specialised laboratory staff.

Impact: e.g. in a surgical trial testing a new technique, the impact should be high (score = 3).

- Occurrence: this depends on the study design.
- Detectability: this depends on the quality of documentation, e.g. in a medical device trial, the level of details of the Instructions for Use (IFU).

## VI. Data

### 21. Volume/complexity

Consider the volume and complexity of data to be collected and if the source data is well identified.

- Impact: this should often be score = 3.
- Occurrence: this should often be score = 3.
- Detectability: this should often be score = 1.

### 22. CRF quality

Consider eCRF vs. pCRF (electronic vs. paper-based Case Report Form), design, and software used (such as automatic checks, rules, or monitor's role).

- Impact: e.g. if the eCRF does not have automatic checks implemented or no queries can be issued, then score = 3.
- Occurrence: this should often be score = 3.
- Detectability: this should be anticipated in order that score = 1.

## VII. Other

### 23. Any other risk:

Consider any additional risks not yet taken into account. The risks should always be balanced against the risks associated with standard medical care for the indications in question.

In the web-version of the RBM Score Calculator, you as the user will be allowed to add as many rows as needed.

## Acronyms and abbreviations

The following acronyms and abbreviations appear in the **Risk-Based Monitoring (RBM) Score Calculator** spreadsheet.

ADR	Adverse Drug Reaction
AE	Adverse Event
ClinO	Ordinance on Clinical Trials in Human Research
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
IFU	Instructions for Use
IMD	Investigational Medical Device
IMP	Investigational Medicinal Product
No.	Number
pCRF	paper-based Case Report Form
PGA	Physician Global Assessment
PI	Principal Investigator
RBM	Risk-Based Monitoring
RF	Risk Factor
SAE	Serious Adverse Event
WHO	World Health Organization



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The Swiss Clinical Trial Organisation (SCTO), together with partner organisations, hosts thematic platforms to promote excellence in clinical research in Switzerland. [www.scto.ch](http://www.scto.ch)

You are welcome to send your feedback on the RBM Score Calculator and these User Instructions to [monitoring@scto.ch](mailto:monitoring@scto.ch)

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