ExHaRM

THE EXERCISE HARMS REPORTING METHOD

PROTOCOL

The Exercise Harms Reporting Method (ExHaRM)

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The Exercise Harms Reporting Method (ExHaRM) provides guidance to improve the quality of harms assessment and reporting for exercise trials.

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ExHaRM
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ExHaRM

THE EXERCISE HARMS REPORTING METHOD

1

MONITOR & IDENTIFY

Participant reports or exercise professional observes adverse outcome.

2

ASSESS & RECORD

Record details of adverse outcome: severity, causality, impact on intervention and type.

3

HARMS PANEL REVIEW

Harms Panel reviews and revises causality of adverse outcomes.

4

ANALYSE & REPORT

All-cause adverse outcomes and exercise-related adverse outcomes are analysed and reported.

RESPOND

Exercise professional provides first aid and manages adverse outcome.

- Include adverse outcome for consideration for exercise participation and prescription.
- Consider external reporting requirements.

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The Exercise Harms Reporting Method (ExHaRM)

Despite a growing recognition of the importance of accurate and comprehensive reporting of the harms of exercise [1], practical guidance on how to manage the collection and reporting process in exercise oncology interventions is missing [2, 3]. Well-accepted standards and guidelines for harms reporting in pharmacological cancer clinical trials exist [4]. However, the direct application of these frameworks to exercise trials, without modification, is inappropriate [5].

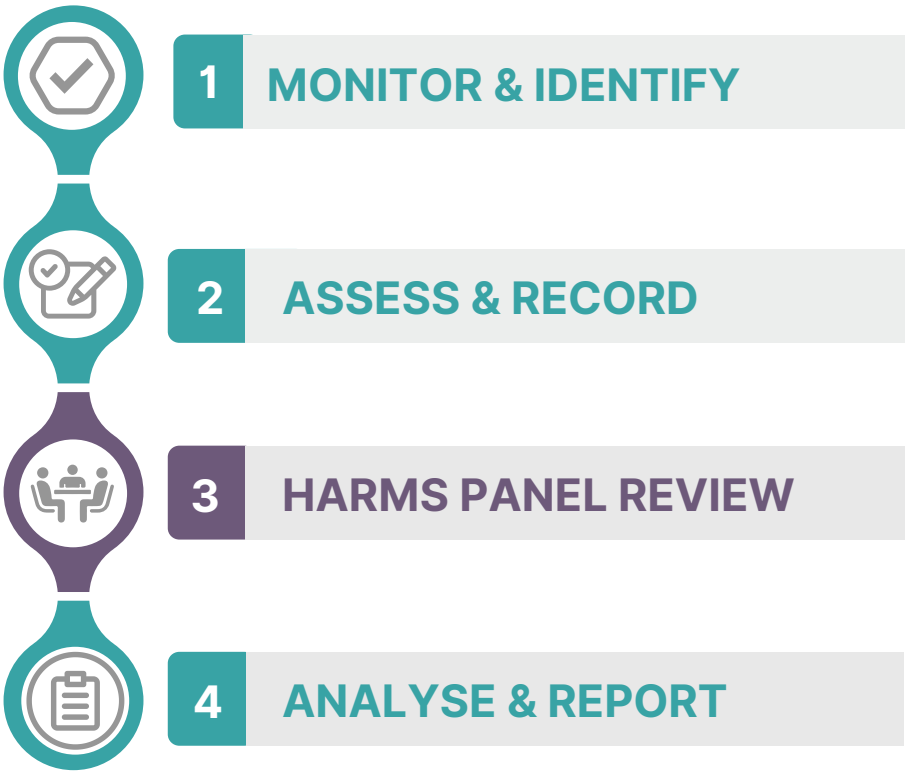
ExHaRM provides guidance to improve the quality of harms assessment and reporting immediately, while concurrently providing a framework for future refinement. Development of the Exercise Harms Reporting Method (ExHaRM) was informed by national and international guidelines for harms reporting in clinical trials involving therapeutic goods or medical devices, with adaptations to enhance applicability to exercise.

The protocol has been adjusted via an iterative process of implementation and adjustment through use in multiple exercise oncology trials involving varied cancer diagnoses (types: breast, brain, gynaecological; stages at diagnosis I-IV; primary/recurrent), and heterogeneous exercise intervention characteristics (face-to-face/telehealth delivery; supervised/unsupervised exercise). Our team first implemented an intentional harm assessment and reporting method in 2015, with the commencement of exercise oncology trials targeting cancer survivors with multiple comorbidities [6] or undergoing intense treatment [7]. It has also involved the development of terms (such as, adverse outcomes, which capture all undesirable physical, psychological, social and economic outcomes) that facilitate the harms assessment process in exercise.

Further, ExHaRM has been used in studies that involve mixed-mode exercise (aerobic and resistance training) delivered during and following treatment, via mixed modes of delivery (face-to-face supervision ranging from 2 sessions/week to 1 session/month, in addition to trials delivered via tele-health) and a range of settings (e.g., exercise completed at participant's homes, community fitness centres, and university, exercise clinics).

The purpose of this protocol is to guide the collection and reporting of reliable, complete, and informative data on the harms of exercise, through an efficient and reasonable method.

ExHaRM involves: Step 1: Monitor occurrence of adverse outcomes through systematic and non-systematic surveillance; Step 2: Assess and record adverse outcomes, including severity, causality, impact on intervention and type; Step 3: Review of causality by harms panel (and revise as necessary); and Step 4: Analyse and report frequencies, rates and clinically meaningful details of all-cause and exercise-related adverse outcomes.



Note: Key terms, including their definitions and related information (e.g., prompts or questions to ensure accurate data collection, and coding recommendations to aid efficient recording) are denoted by underline throughout this protocol and can be found at the end of this document.

1 MONITOR & IDENTIFY

Systematically monitor and identify Adverse Outcomes (AOs):

- Actively prompt participants to report adverse outcomes. Use standardised language and standardised recall periods. For example, the exercise professional asks the participant at every contact: "Since our last session have you experienced any harmful or undesirable outcomes, whether or not you think they were caused by exercise? For example, have you had an injury or worsening of an old injury, or any unusual or worsening treatment-related symptom?" (i.e., active surveillance)
- Train exercise professionals to actively observe for adverse outcomes that may occur during supervised exercise, and to probe during discussions if a participant reports something that might be an adverse outcome (i.e., passive surveillance / spontaneous reporting of adverse outcomes).
- Consider generating a study-specific list of adverse outcomes of interest that are systematically recorded via a checklist or standardised test at fixed time points (systematic surveillance), in addition to the broad question recommended above (non-systematic surveillance).

RESPOND

Whilst not part of the harms-reporting process, the exercise professional has a duty of care to the participant to identify, consider and manage all adverse outcomes and depending on the nature of the adverse outcome (with particular attention required for adverse events) may have external reporting requirements:

- a) Provide first aid and management of the adverse outcome: Respond to immediate needs of the participant through administration of first aid, cessation or modification of exercise, referral to other health professional, and/or other responses as required.
- b) Complete tasks as per exercise professional duties and scope of practice: Consider whether adverse outcome requires an absence from exercise (i.e., is it a contraindication?) and/or modification of exercise parameters (e.g., volume, intensity, or type).
- c) Report as per requirements of employer, institution, funding and / or ethics committees.

Note: The definitions (e.g., of harms, adverse outcomes, and severity) in this protocol are those determined to be most appropriate to the evaluation of exercise-related harms. Regulatory committees (e.g., a human research ethics committee) typically require the reporting of “serious adverse events” only, which will be captured within the monitoring and reporting of adverse outcomes as outlined in this protocol.

2 ASSESS & RECORD

Assess and record the adverse outcome and associated classifications of severity, causality, impact of adverse outcome on the intervention, and type of adverse outcome, including sufficient detail to justify the assigned category. Also record detail of the context and sequalae of the adverse outcome; for example, where and when the adverse outcome occurred, what clinical action was taken, the duration of the adverse outcome and any subsequent treatment.

Severity (Grade 1-5): based primarily on the resultant medical treatment and the impact of the adverse outcome on activities of daily living.

Causality: based on the timing of the adverse outcome in relation to exercise and plausibility of relationship with exercise or other factors (see useful questions to consider under “Causality”). Include both the participant’s opinion and exercise professional's judgement of causality.

Impact on intervention: based on changes to a participant’s involvement in the exercise intervention caused by the adverse outcome. This may involve modifications (e.g., modified exercise prescription, missed exercise sessions), or absences from the intervention (either temporary or permanent).

Type of adverse outcome: the purpose of categorising adverse outcome by type is to create groupings for simplified summary based on predetermined categories (e.g., abnormal response to exercise, injury, exacerbation of treatment-related side effect).

> Note: Care should be taken to differentiate between a persistent and recurrent adverse outcome, as persistent adverse outcomes need only be reported once, whereas recurrent adverse outcomes should be reported at each recurrence.

3 HARMS PANEL REVIEW

The attribution of causality (i.e., determining which adverse outcomes are causally related to exercise) is essential to the evaluation of exercise-related harms. Causality attribution requires knowledge of the mechanisms by which an intervention may cause harm, as well as the expected responses to an intervention (i.e., scope of exercise professional). Concurrently, an understanding of what is common and expected in the population (both disease- and treatment-related) is also required and is likely most appropriately provided by the medical team. Therefore, while it is appropriate for exercise professionals to make the initial judgement of causality, ideally adverse outcomes should be reviewed by a panel with additional expertise, and preferably at least one individual who is not directly involved in the study.

All adverse outcomes are reported to the study harms panel on a pre-determined schedule. This may be frequently (e.g., monthly) or at a single point prior to data analysis.

The harms panel review all adverse outcomes with special attention to:

- unusual or unanticipated adverse outcomes (as judged by panel);
- discordant opinions of causality recorded between participant and exercise professional;
- adverse outcomes ≥ grade 3.
- adverse outcomes that the exercise professional has highlighted for review

Discrepancies in causality attribution between exercise professional and any member of the harms panel should be discussed, and the consensus reached by the panel be recorded as the final causality decision.

The harms panel may also determine that a reported adverse outcome does not meet the definition of an adverse outcome (e.g., the recorded event might not be judged by the panel as being undesirable). In this situation the adverse outcome would be removed from the dataset and would not be reported.

4 ANALYSE & REPORT

Data preparation and analysis

- Any adverse outcome with a causality of certain, likely, or possible is categorised as an exercise-related adverse outcome. The term "all-cause adverse outcomes" is then used to refer to adverse outcome of any causality (i.e., all adverse outcomes: those deemed exercise related, as well as those not attributed to exercise).
- Re-code adverse outcomes with standardised language: each adverse outcome identified in the study should be described using standardised language (e.g., Medical dictionary for Regulatory Activities [MedDRA®] [8] preferred terms) and summarised (e.g., within system organ class or appropriate groupings). For example: a report of "stiff and sore shoulders" as an adverse outcome in the clinical notes could be coded as "arthralgia" using MedDRA terminology and listed under the category of "Musculoskeletal and Connective Tissue Disorders", along with other conditions, such as arthritis.
- Group all-cause adverse outcomes and exercise-related adverse outcomes by each category of Type of Adverse outcome and Impact on intervention.

Reporting

All-cause and Exercise-related adverse outcomes:

- Report the number of all-cause adverse outcomes and exercise-related adverse outcomes, including the number (and proportion) of all-cause adverse outcomes and exercise-related adverse outcomes categorised by severity as mild-moderate (grades 1 and 2) and severe (grades 3-5).
- For these harms outcomes (i.e., number of all-cause adverse outcomes and exercise-related adverse outcomes by severity categories) it is helpful to also report the number of participants (and proportion of all participants) reporting an adverse outcome at least once.
- The number of adverse outcomes (and percentage) for each MedDRA code (e.g., arthralgia) and system organ class (e.g., musculoskeletal and connective tissue disorders), or other standardised language groupings, should be reported for all-cause adverse outcomes and for exercise-related adverse outcomes.

4 ANALYSE & REPORT CONT.

Exercise-related adverse outcomes only:

- The number (and proportion) of exercise-related adverse outcomes in each category of 'impact on intervention' and 'type of adverse outcome' should be reported.
- Highlight any unique or key exercise-related adverse outcomes relevant to the context of the study, or of clinical relevance (e.g., lymphoedema, dislodged peripherally-inserted central catheter, bone fractures).
- Consider reporting exercise-related adverse outcomes as a rate per person per week of intervention, in conjunction with the average weekly minutes of exercise that were completed. If rate is not reported, then ensure sufficient intervention and trial details are included to allow subsequent studies to compare results.

Adverse outcomes that occur during exercise testing (i.e., objective data collection) should be reported separately to those that occur during the intervention.

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Definitions

Active surveillance of harms	Participants are asked via structured questionnaires or interviews about the occurrence of adverse outcomes, or laboratory or other diagnostic tests which are performed at prespecified time intervals. In the most basic form, this may involve asking the participant or exercise professional about the occurrence of "any undesirable occurrences" at set-time points during the study.
Adverse event	Adverse event is the most common measurement tool in harms reporting across disciplines. Adverse events are any harmful or undesirable medical occurrence that occurs during participation in an intervention, irrespective of whether there is a causal relationship with the intervention. A medical occurrence may include (but is not limited to): • an acute injury; • exacerbation of a chronic or past injury; • new treatment-related side effect or symptom; • increase in severity of treatment-related side effect or symptom; • study withdrawal; • early termination of treatment; • disease progression or death from disease during intervention period [9].
Adverse Outcome	An adverse outcome is any undesirable physical, psychological, social and economic outcome, experience or event. Adverse outcomes are all undesirable occurrences, irrespective of whether there was a causal relationship between the outcome and the intervention.

Definitions cont.

Adverse Outcomes of interest

Adverse outcomes that are important to the consumer (people living with and beyond cancer), clinicians (medical and exercise professional) and decision makers.

Adverse outcomes of interest are determined based on previous evidence of the harms of specific exercise (e.g., mode, intensity) in a given population (i.e., oncology and haematology). These often include: the most clinically serious adverse outcomes, common adverse outcomes, and adverse outcomes of importance to stakeholders and patients.

Examples of adverse outcomes of interest:

- fracture rates in a population with pre-existing bone lesions (data collected via validated self-report questionnaires or extracted from medical records),
- newly diagnosed or exacerbated lymphoedema (this may be recorded by participants being prompted to report results of standard surveillance by their medical team or through study-specific testing, e.g., using bioelectrical impedance spectroscopy at pre-determined time points),
- issues with stomas or peripherally-inserted central catheters (data collected from medical records or prompted self-report at set time points).

For some adverse outcomesof interest it may be possible to collect data from the control and exercise groups, allowing comparison of risk.

Collecting adverse outcomesof interest should not exclude the active surveillance of other adverse outcomes, particularly given that what is important varies between individuals and situations.

All-cause adverse outcomes

All-cause adverse outcomes are all adverse outcomes identified in a trial, regardless of causality attribution. All-cause adverse outcomes = non-exercise-related adverse outcomes + exercise-related adverse outcomes.

Definitions cont.

Causality

Causality describes the likelihood that an adverse outcome was caused by exercise, as judged by the exercise professional delivering the exercise intervention (or Harms Panel). Causality attribution is based on a range of factors, including the timing of the adverse outcome in relation to exercise versus other factors, the biological plausibility of the relationship and the expectedness of the adverse outcome (with regard to the nature, severity and frequency of the outcome) in the population being studied (i.e., is the adverse outcome an expected outcome of disease or treatment and therefore likely to occur even in the absence of exercise?).

Categories:
C = Certain: adverse outcome occurred within a plausible time relationship to completed exercise and cannot be explained by concurrent disease, treatment, or other drugs.

L = Likely: adverse outcome has a reasonable time sequence to completed exercise and unlikely to be attributed to concurrent disease, treatment, or other drugs. [sometimes termed “probable”, ExHaRM preferentially uses “likely” to reduce potential data errors due to confusing probable and possible]

P = Possible: adverse outcome has a reasonable time sequence to completed exercise but could also be explained by concurrent disease, treatment or other drugs.

U = Unlikely: adverse outcome has a temporal relationship to drug administration, treatment, or other medical event which makes a causal relationship with completed exercise improbable but not impossible, and other drugs or underlying disease provide a plausible explanation.

NR = Not related: adverse outcome has no temporal relationship with exercise and/or adverse outcome has been attributed by other health professional to another cause (e.g., underlying disease or drug)

Definitions cont.

Causality cont.

UC = Unclassified: This category should only be used when there is no way to categorise the adverse outcome. An exercise professional may use the term to identify an adverse outcome as requiring classification by the harms review panel, particularly when the exercise professional does not have appropriate scope or expertise to judge causality. Adverse outcomes recorded as unclassified by the exercise professional must be classified by the harms panel.

Useful questions for exercise professional or Harms Panel to consider when attributing causality include:

1. Is the adverse outcome a previously identified or a known response to exercise?
2. Has the adverse outcome occurred previously in this study (in this or another participant)?
3. Does the adverse outcome improve or stop when exercise is ceased?
4. Does the adverse outcome reoccur when exercise is re-commenced?
5. Is there a temporal relationship between the adverse outcome and exercise? Did exercise precede the adverse outcome and did the adverse outcome appear at an appropriate time interval after exercise (e.g., did the adverse outcome occur during exercise, or during a period post exercise that would mechanistically link the adverse outcome with the exercise. The post-exercise period may differ based on the specific adverse outcome. For example, a vasovagal episode is more likely to occur immediately post-exercise, whereas delayed-onset muscle soreness is more likely to occur 24-48 hours post-exercise)
6. Was the adverse outcome present at the beginning of the study (i.e., prior to commencing intervention / exercise)?
7. Can the participant's underlying clinical disease state (or comorbidities) explain the adverse outcome?
8. Are there any other potential causes for the adverse outcome?

(Questions adapted from "Oncology Clinical Trials: successful design, conduct and analysis" [10] and World Health Organisation–Uppsala Monitoring Centre Causality assessment system [11]).

Definitions cont.

Common terminology criteria for adverse events (CTC-AE)

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE) [12] is a descriptive terminology which can be used for harms reporting.

A grading (severity) scale is provided for each adverse event term. These criteria provide standardised language for describing the type and defining the severity of adverse events.

The list of terms was developed to reflect adverse events within the context of medical treatment and therefore does not include a comprehensive list of terms relevant to exercise interventions. ExHarm uses the broad severity rating categories (i.e., grades 1 to 5) to grade the severity of adverse outcomes in the same way the CTC-AE grades adverse events, but primarily relies on MedDRA or other standardised language to describe the adverse outcome.

Exercise-related adverse outcome

An adverse outcome that is judged as having a reasonable causal relationship with participating in the exercise intervention.
Note: 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship. "Reasonable causal relationship" includes the causality classifications of: "Possible", "Likely" and "Certain". (Refer to causality term for full definitions of causality categories and recommended questions for determining attribution.)

Harms panel

The study-specific harms panel review the allocated causality of all adverse outcomes. The composition of the panel will depend on the needs of the study. Most harms panels will include an exercise professional with substantial oncology experience, a medical oncologist, surgeon and/ or nurse, and senior research staff. It is preferable to include at least one member of the panel who has no other involvement in the study.

Definitions cont.

Impact on intervention

The impact of the adverse outcome describes how the participant's involvement in the intervention (i.e., exercise) is changed because of the adverse outcome.

Categories:

- M1: modified exercise prescription (frequency, intensity, type, duration, volume)
- A1: adjusted frequency of contact (e.g., increased or decreased frequency of contact with exercise professional),
- TI 2: temporary interruption from the intervention (contact and exercise),
- PW 2: permanent withdrawal from intervention (with or without withdrawal from the study),
- D: Death

1 Adjusted frequency of contact and modified exercise prescription may occur concurrently.
2 Permanent withdrawal and temporary interruption may need to be coded or recoded retrospectively.

Medical dictionary for Regulatory Activities (MedDRA®) [8]

MedDRA® is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). It provides a standardised method to describe medical events. Using standardised language allows for comparison between studies and aggregate reporting via meta-analyses.

MedDRA is searchable via a browser which is accessible via internet, mobile device or desktop (https://www.meddra.org/). Access requires a subscription which is free of charge for non-commercial / not for profit organisations.
MedDRA® trademark is registered by ICH.

A limitation of MedDRA is that it is medical terminology and does not capture some outcomes, such as abnormal responses to exercise. Study-specific language lists can be developed for use in instances that are not able to be described by MedDRA.

Definitions cont.

Non-systematic surveillance of harms	Collection of adverse outcomes that does not use a systematic approach (i.e., researchers do not ask about specific adverse outcomes or apply standardised testing). This approach usually involves asking participants to report the presence of adverse outcomes they have noticed (this can be through active or passive surveillance).
Passive surveillance of harms	Participants are not specifically asked about or tested for the occurrence of adverse outcome. Rather, adverse outcomes are identified based on participant or exercise professional reports made on their own initiative. This is also called spontaneous reporting.
Persistent adverse outcome	A persistent adverse outcome is an adverse outcome that extends continuously, without resolution. The adverse outcome is reported only once unless the grade changes. If the grade becomes more or less severe the adverse outcome is reported again, as a new adverse outcome with the new grade.
Recall period	The period between each occasion of adverse outcome reporting (by participant or clinician). E.g., If the exercise professional asks the participant to report any adverse outcomes that have occurred since the previous session that was 7 days ago, then the recall period would be 7 days.
Recurrent adverse outcome	A recurrent adverse outcome is an adverse outcome that occurs and resolves. An adverse outcome that resolves and then recurs should be reported at each recurrence.
Serious adverse event	The term Serious adverse event has not been used in in ExHaRM. We acknowledge the term here as it is often a reporting requirement of ethics or institutional boards. Serious adverse events are adverse events that meet a specific definition, separate to severity. The term is primarily used in defining regulatory reporting obligations for clinical trials. In ExHaRM adverse events are captured by the umbrella term adverse outcome. Adverse outcomes are divided by grade into mild-moderate (grade 1-2) and severe (≥ grade 3), rather than being defined as serious and non-serious.

Definitions cont.

Serious adverse event cont.

Serious adverse events [14] are any exercise-related adverse events (i.e., "undesirable medical occurrences") occurring at any dose of an intervention that results in ANY of the following outcomes:

1. Death.
2. A life-threatening experience.
3. Inpatient hospitalization or prolongation of existing hospitalization (for >24 hours).
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Reporting requirements are usually determined by ethics or institutional boards and in most cases there are specific reporting requirements for serious adverse events. Given clinical and legal implications of these events, it is recommended that all exercise interventions and programs have a process requiring exercise professionals to report these serious adverse events to senior staff.

Further, it is recommended that any adverse outcomes that meet the above definition should be reported to supervisors/ senior staff for review, regardless of whether the exercise professional judged the event to be exercise-related. It is recommended that serious adverse events (or adverse outcomes where causality could not be confidently assessed, but that otherwise met any serious adverse event criteria) are reported to the harms panel within 48 hours for immediate review.

Definitions cont.

Severity / Grade

Adverse outcomes are given a severity rating based on a grading scale of 1-5 (as per CTC-AE). Severity may also be grouped into categories of mild-moderate (grade 1-2 adverse outcomes) or severe (grade 3-5 adverse outcomes). Note: A severe adverse outcome, is NOT the same as serious adverse event which is defined separately (see “serious adverse events”)

Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; medical treatment not indicated. ExHaRM application: “no/minimal disruption to activities of daily living”

Grade 2 - Moderate; minimal, local or noninvasive medical treatment indicated; limiting age-appropriate instrumental activities of daily living. [Instrumental activities of daily living refer to activities such as preparing meals, shopping for groceries, using the telephone, managing money, etc.] ExHaRM application: “some disruption to instrumental activities of daily living”

Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; substantially limiting self-care activities of daily living. [Self-care activities of daily living refer to activities including bathing, dressing and undressing, feeding self, using the toilet, taking medications.] ExHaRM application: “complete disruption to self-care activities of daily living”

Grade 4 - Life-threatening consequences; urgent medical treatment indicated.

Grade 5 - Death related to adverse outcome.

Definitions cont.

Systematic surveillance of harms	Asking every participant (at defined time points) about specific adverse outcomes or performing specific laboratory or other diagnostic tests. Systematic surveillance is, by definition, one approach to active surveillance of harms. Systematic methods, such as querying participants using a comprehensive checklist or standardized laboratory tests, are more likely than non-systematic methods to identify all occurrences of an adverse outcome.
Type of adverse outcome	Relevant categories of Type of adverse outcome may depend on the type of intervention and any harms of interest collected. Example list and reporting codes • Ex: normal response to exercise (e.g., DOMS), • AbEx: abnormal response to exercise, • SE: expected disease- or treatment-related side effect, • SE+: exacerbation of disease- or treatment-related side effect, • In: injury, • O: other (describe)