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Update on ISO 14155 and 18969

Danielle Giroud
CEO, MD-Clinicals

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About the speaker

About Us

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With services tailored to your specific needs, we offer flexible solutions that are as unique as your product - to assure you the quickest and most effective path to market.

We're passionate about medical devices and IVD.

With over 35 years of experience in managing medical device/IVD clinical investigations around the globe, we have what it takes to move your product to market swiftly and cost-effectively, saving you precious time and money in the process.

Our unsurpassed clinical and regulatory expertise in medical device and in-vitro diagnostic market access is there to answer all your questions.

With **over 30 successful MDR approvals** including EU expert panels passed without any comments, we work with clients hand in hand to make things work.

About Me

Danielle Giroud

- 40 years of experience within the medical device and in-vitro diagnostic industry,
- Founder and CEO of MD-Clinicals (https://www.md-clinicals.com), a medical device and in-vitro diagnostic-focused CRO with offices in Switzerland, Frankfurt, and Beijing.
- Founder and CEO of WMDO – online learning for medical device professionals (https://www.wmdo.org)
- Since 1998, convener for the expert group on clinical investigations (TC 194 WG4) for the ISO 14155 and 18969 on clinical evaluation.

And there is still so much to do!

Firm believer in regulatory convergence

Update ISO 14155

ISO 14155:2020 – update risk management considerations

Risks related to the **use of the** investigational device (6.2.1)

For the investigational device including any applicable clinical procedure related to its use (see 6.2.2), the sponsor shall predefine or establish risk acceptability thresholds and trigger a risk assessment to determine whether actions are needed as soon as thresholds are reached or exceeded (see Annex H).

NOTE 3 Risk acceptability thresholds related to the use of the investigational device are normally derived from the expected incidence of harm. In a clinical investigation such a harm is considered to be an adverse device effect.

ISO 14155:2020 – update risk management considerations

Residual risks, associated with the use of the investigational device shall be evaluated, proportionate to the clinical investigation sample size/population, in accordance with ISO 14971 prior to design and conduct of a clinical investigation (see Annex H). This risk evaluation shall include or refer to an objective review of published and unpublished medical and scientific data. The residual risk evaluation should be relevant to the targeted indication(s) and population(s) under investigation.

NOTE 1 It is acknowledged that the observed occurrence rate of adverse device effects can differ between a clinical investigation and rates in the general population, due to reporting rates, specifics of the patient population, indications and sample size of the clinical investigation.

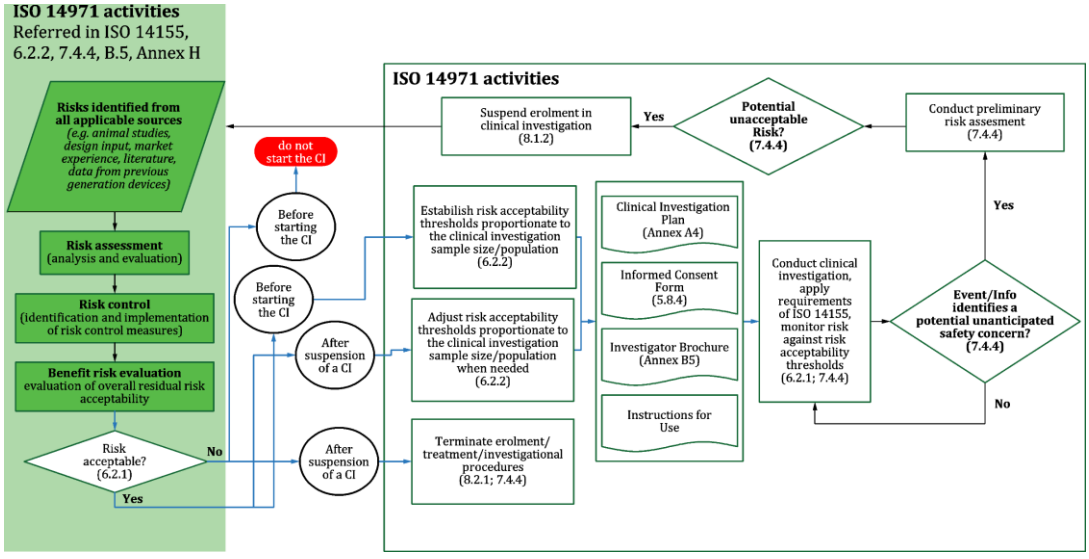
ISO 14155:2020 – update risk management considerations

Risks related to the **use of the** investigational device (6.2.1)

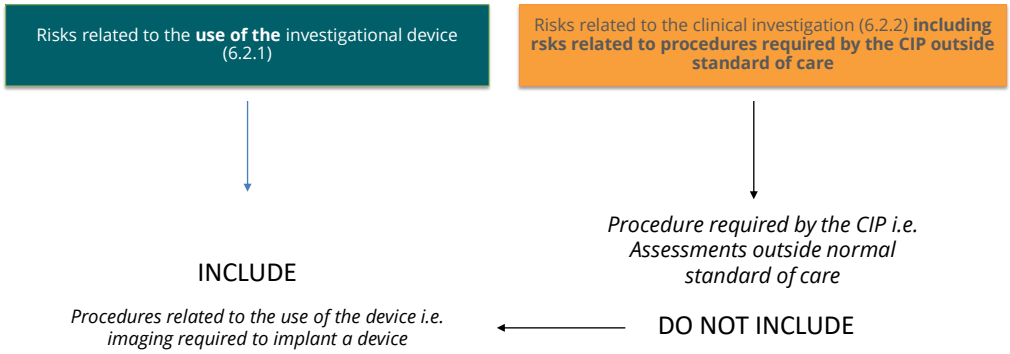
Annex H update

- *Adjustment of risk acceptability criteria from RA to study population proportion*
- *Adapted flow before and after start of study*

ISO 14155:2020 – update risk management considerations



ISO 14155:2020 – update risk management considerations



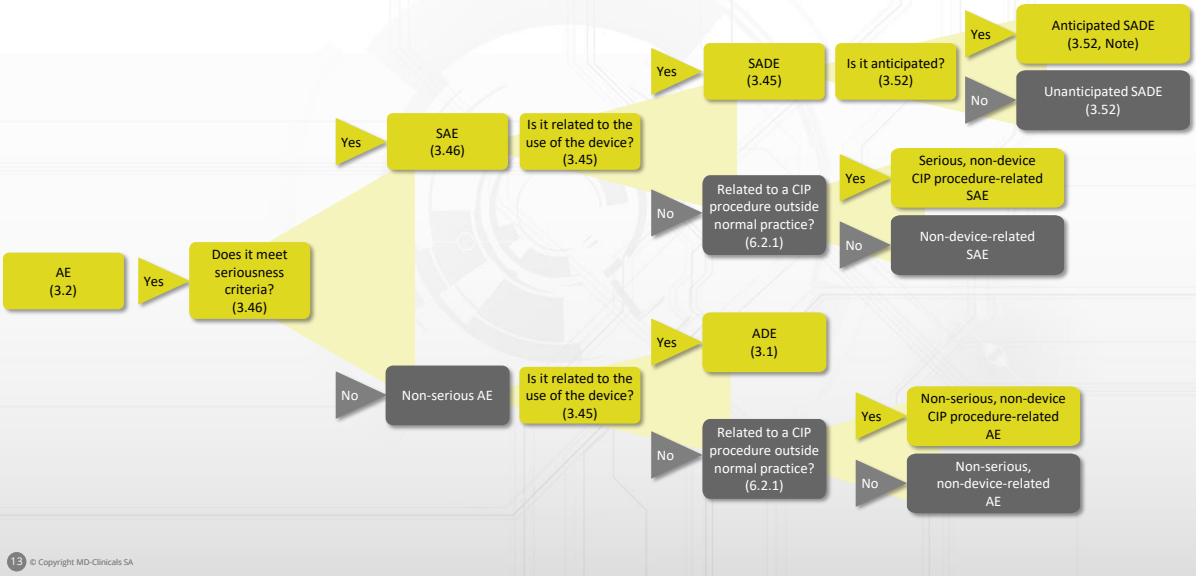
ISO 14155:2020 – update risk management considerations

New section 7.4.5: Management of risks related to the clinical procedures required by the CIP

A risk based approach shall be applied to the clinical procedures required by the CIP that are additional to normal clinical practice (see clause J.6 and 6.2.1 Note 2). Should potentially unacceptable risks arise, then the sponsor should consider suspending and consider corrective actions or terminating the clinical investigation (see 8.2).

After suspension, in certain cases, the necessary corrective actions may require an amendment of the CIP before resuming the clinical investigation (see 8.2.4).

ISO 14155:2020 – Annex F AE categorization



ISO 14155:2020 – Estimands

Annex K (new): Clinical Investigation Design considerations

An estimand is a precise description of the treatment effect reflecting the clinical question posed by the clinical investigation objective. It summarises at a population-level what the outcomes would be in the same subjects under different treatment conditions being compared. 'Compared' does not necessarily refer to more than one treatment group in a given clinical investigation but could mean comparisons with clinical data from the literature clinical data covering no treatment or prior to current standard of care.

ISO 14155:2020 – Estimands

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Annex K (new): Clinical Investigation Design considerations

The statistical analysis of clinical investigation data (as described in Annex A.7) may be aligned to the estimand(s). In the statistical analysis plan, the section on analysis population may be refined by considering the following:

a) Estimands for all objectives, i.e., sets of attributes such as:

1) treatment condition of interest and, as appropriate, the alternative treatment condition to which comparison will be made,
2) population of patients targeted by the clinical question,
3) endpoint(s),
4) intercurrent events
5) population-level summary for the endpoint that provides a basis for comparison between treatment conditions.

ISO 14155:2020 – Estimands

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— Example of estimand and its attributes

ESTIMAND	Treatment effect on pain reduction in patients with chronic pain
Treatment	The use of a novel pain management medical device
Population	Adult patients with chronic lower back pain who initiated treatment
Variable and timepoint (endpoint)	The primary outcome variable is the *reduction in pain intensity*, measured using a visual analog scale (VAS), after 12 weeks of treatment.
Intercurrent events	If a patient discontinues the treatment for any reason (e.g. adverse events or lack of effectiveness), their pain scores will be considered up to the point of discontinuation or their pain score will be considered ‚worst pain score'. This ensures that the observed data reflects the potential impact of the treatment.
Missing data	If a patient misses a scheduled pain assessment, multiple imputations or another appropriate method will be used to impute missing values to account for potential bias.

ISO 14155:2020 – Other updates

A.1 clinical performance

ability of a *medical device* (3.35), resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for *subject(s)* (3.51), when used as intended by the manufacturer Note 1 to entry: Clinical performance can be defined under national regulations.

ISO 14155:2020 – Other updates

Section 5: deviation vs amendment

A request for deviation in eligibility criteria does not constitute a deviation but must be done via a protocol amendment

↓

To ensure scientific validity of the clinical investigation

ISO 14155:2020 – Other updates

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Clause 5.8.1 (informed consent – General)

Informed consent shall be obtained in writing from the subject or where applicable, the subject's legally designated representative and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject, except when special circumstances described in 5.8.3.4 apply.

ISO 14155:2020 – Other updates

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Clause 5.8.2 (informed consent – Process for obtaining...)

e) provide ample time for the subject to read and understand the informed consent form and to if desired, discuss with others e.g. family members to consider participation in the clinical investigation;

ISO 14155:2020 – Other updates

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6.11 Data monitoring committee (DMC)

The sponsor shall consider establishing a DMC prior to starting the clinical investigation.

The decision to establish a DMC shall be guided by the risk assessment, taking into account both the risks associated with the use of the investigational device and the risks associated with subject's participation in the clinical investigation.

The primary function of the DMC shall be described in the CIP.

The sponsor or DMC shall establish a Charter to document the following but not limited to:

a) the responsibilities and scope of activities of the DMC;

b) the frequency, format, and documentation of meetings;

c) arrangements for handling emergency situations;

d) confirm conditions for suspending or stopping the clinical investigation, if relevant for safety management (see clause A.16 a)).

ISO 14155:2020 – Other updates

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3.7
Clinical events committee
CEC
independent committee of clinical experts that can be established by the sponsor to ensure consistent event assessment across participating centres and mitigate inadequate reporting risks

Note 1 to entry: For the purpose of this document, "central events committee", ''clinical adjudication committee (CAC)'', ''endpoint adjudication committee (EAC)'' are synonymous with CEC.

ISO 14155:2020 – Other updates

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6.12 Clinical events committee (CEC)

The sponsor shall consider establishing a CEC prior to starting the clinical investigation.

The decision to establish a CEC can be driven by the need to reduce the impact of potential variability on conclusions drawn from outcomes data.

The sponsor or CEC shall establish a Charter to document the following but not limited to:

— Methods for central review and classification of safety or effectiveness endpoints in a unbiased, confidential and consensus-based manner;

— Criteria for determining whether potential endpoints meet CIP definition and endpoints;

— Ensure standardized endpoint outcomes for statistical analysis;

— Classify events (including serious adverse device effects, device deficiencies) as related to the use of investigational device or clinical procedures required by the CIP, their expectedness.

ISO 14155:2020 – Other updates

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9.2.2 Preparation of documents and materials

Prior to commencement of the clinical investigation, the sponsor shall

a) prepare the documents, as described in clause 5, clause 6, and clause 7, and ensure they are approved by the relevant persons by dated signature; if required, copies shall be provided to all parties involved, and dated signatures obtained as appropriate,

b) ensure the accuracy of the translation, where relevant,

c) ensure that a supply of investigational devices, as characterized in 7.9, is available in a timely manner for the clinical investigation; investigational devices shall not be made available to the principal investigator until all requirements to start the clinical investigation are met,

d) establish a procedure assuring device accountability, which enables the immediate identification and where necessary, the recall of devices used in the clinical investigation,

e) if appropriate, prepare template for implant card for investigators to provide to subjects after implantation

ISO 14155:2020 – Other updates

B2 : Investigator Brochure: Investigational device information

Added:

h) Information on training on the use of the investigational device and where applicable proctoring

ISO 14155:2020 – Other updates

B.3 Preclinical testing

Summary of the preclinical testing that has been performed on the investigational device, together with an evaluation of the results of such testing, justifying its use in human subjects.

The summary shall include or, where applicable, refer to the results of

a) design calculations,

b) in-silico tests,

c) *in vitro* tests,

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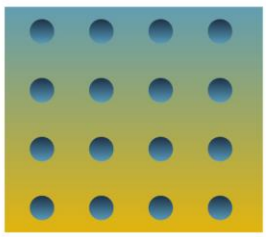
ISO 14155:202**4**

Timelines:
DIS – Jun 2024
FDIS – Q4 2024

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Update ISO 18969

ISO 18969 – Objectives of the Working Group

Disclaimer: the text provided in this presentation is part of early drafting and may be subject to change before a first draft document is published. This presentation is reflecting a personal opinion which may not be shared by all WG members.

- Provide guidance on a clear methodology for conducting clinical evaluation for medical devices
- Integrate or make the link between the clinical evaluation and other processes such as risk management, design validation etc,
- Serve multiple purposes i.e. not solely clinical evaluation for CE-mark
- Provide a uniform template that aligns parties.

ISO 18969 - Scope

The document specifies terminology, principles and process for the clinical evaluation of medical devices. This document provides guidance on how to gather, appraise and analyse data to assess the safety, clinical performance or effectiveness of medical devices, and to evaluate the acceptability of clinical risks in the light of the clinical benefits achieved when the device is used as intended by the manufacturer.

ISO 18969 – Key Concepts

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1

Useful:
The clinical evaluation process must start during the design and development phase to support:

- defining the intended use
- identifying endpoints
- identifying risks and potential benefits
- Identifying performance or effectiveness variables
- Establish acceptance criteria

ISO 18969 – Key Concepts

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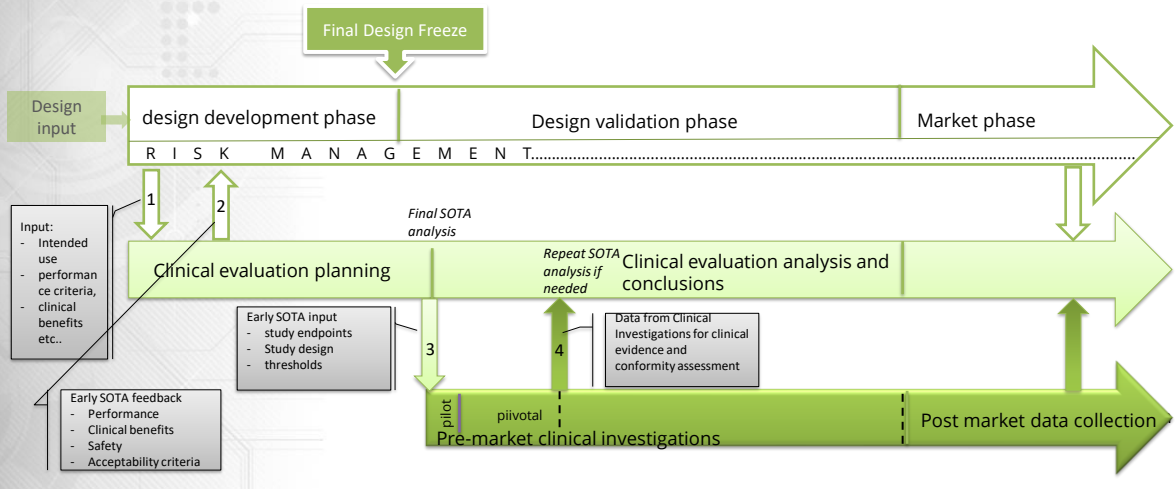

Note that 1 and 2 may be a repetitive exercise till design freeze

ISO 18969 – Key Concepts

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2

Support:
The clinical evaluation process must be an integrated process in overall product development to support:

- design and development with data from literature
- risk management with meaningful quantitative and qualitative data
- provide input in pre-market clinical investigations as part of the validation process

ISO 18969 – Key Concepts

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3

Integrated:
The clinical evaluation process must be an integrated process in overall product development to support:

- design and development with data from literature
- risk management with meaningful quantitative and qualitative data
- provide input in pre-market clinical investigations as part of the validation process

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ISO 18969

Timelines:
First WD – jun 2024
CD: earliest Q4 2024

As promised last year, soon to come...

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We hope to welcome you:
- As a member
- As a contributor
- As a volunteer

Contact

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Questions & Answers

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Thank you!

Now is the time to ask that question you had five slides back. ☺

