Concept of National Regulatory Authority's Maturity Level, WHO-Listed Authority's Performance in the Context of Clinical Trials Oversight: **Part II**

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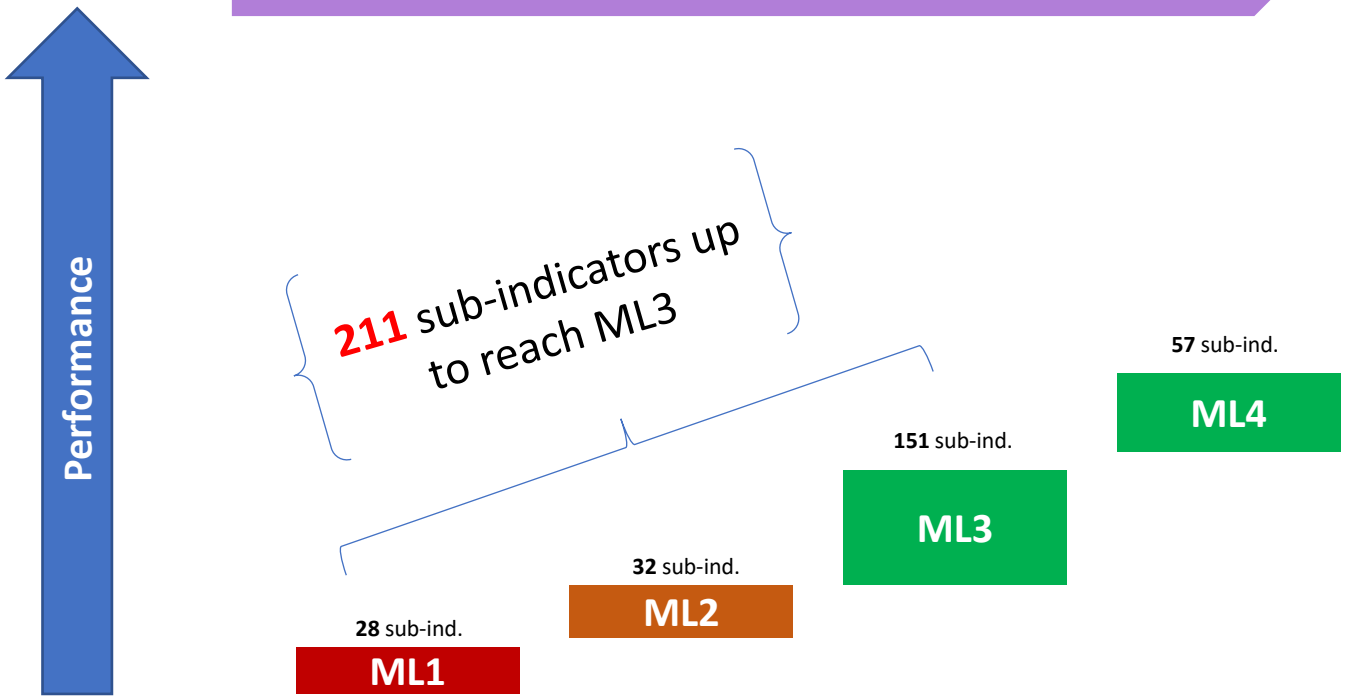
Learning Objectives

1. What are GBT indicators and sub-indicators for Clinical Trials Oversight (CTO)?
2. What are Indicators and Tools for WLA Performance Evaluation for CTO?

WHO GBT Indicators for Assessing Clinical Trials Oversight (CTO)

NRA-ML What's being measured?

NRA Maturity Defined by Benchmarking using GBT



How well a regulatory system is configured?

ML: maturity level; **PE:** performance evaluation; **MA:** registration & marketing authorization; **VL:** vigilance; **RI**: regulatory inspections; **LT:** laboratory testing; **CT:** clinical trial oversight

Source: WHO RSS

Regulatory Functions & ML Sub-indicators in WHO NRS GBT

Function Name	ML 1	ML 2	ML 3	ML 4	Total	Key Focus Areas
01. National Regulatory System (RS)	4	7	27	22	60	Legal framework, governance, QMS, HR
02. Registration & Marketing Authorization (MA)	6	2	23	4	35	MA process, renewal, transparency
03. Vigilance (VL)	5	3	14	4	26	ADR reporting, risk management, feedback
04. Market Surveillance & Control (MC)	3	4	15	5	27	Import/export, SF products, transparency
05. Licensing Establishment (LI)	2	1	13	3	19	Licensing, inspection, HR, transparency
06. Regulatory Inspection (RI)	3	2	13	8	26	GXP enforcement, inspection, QMS
07. Laboratory Testing (LT)	2	2	18	6	28	NCL, QMS, infrastructure, safety
08. Clinical Trial's Oversight (CT)	**2**	**8**	**17**	**3**	**30**	**CT authorization, ethics, reporting**
09. NRA Lot Release (LR)	1	3	12	1	17	Lot release, records, performance
Total	**28**	**32**	**152**	**56**	**268**	

Clinical Trials Oversight (CTO): A summary description

Purpose of Clinical Trials Oversight

Protecting participant rights, safety, and well-being is the core goal of clinical trials oversight.

Regulatory and Ethical Frameworks

Oversight aligns with global standards like Declaration of Helsinki, Nuremberg Code, and ICH GCP guidelines.

Ensuring Data Integrity

Maintaining scientific validity and preventing fraud and data falsification in clinical research processes.

Strengthening Regulatory Capacity

Empowering authorities to effectively manage clinical trials and respond to public health emergencies.

CTO indicators

CT01 **Legal provisions, regulations and guidelines** required to define regulatory framework of clinical trials oversight.

CT02 Arrangement for **effective organization and good governance**

CT03 **Human resources** to perform clinical trials oversight activities.

CT04 **Procedures** established and implemented to perform clinical trials oversight.

CT05 Mechanism exists to promote **transparency, accountability and communication**.

CT06 Mechanism in place to monitor **regulatory performance and output**.

CT01 Legal provisions, regulations and guidelines required to define regulatory framework of clinical trials oversight (1)

CT01.01: **Legal provisions and regulations** for **clinical trials (CTs) oversight** exist.	**ML 1**
CT01.02: **Legal provisions and regulations** that stipulates that authorization from NRA and notification to the NRA is required for **any changes or variations (i.e., amendments)** in the original protocol or in any relevant documents of the CT.	**2**
CT01.03: **Legal provisions and regulations** requiring research centres, researchers, sponsors, clinical research organizations (CROs) and all relevant institutions in the clinical trial to comply with **good clinical practice (GCP)**	**2**
CT01.04: **Legal provisions, regulations and guidelines** requiring that investigational medical products (IMPs) comply with **good manufacturing practice (GMP) for IMPs**	**3**
CT01.05: There are legal provisions or regulations covering circumstances in which **the routine CT evaluation and procedure may not be followed** (e.g. for public-health interests)	**2**
CT01.06: **Legal provisions, regulations or guidelines** exist for NRA to **inspect, suspend or stop CT**	**3**

CT01 Legal provisions, regulations and guidelines required to define regulatory framework of clinical trials oversight.

CT01.07: There are legal provisions and /or regulations that require the establishment of **an independent ethics committee (IEC)**	**ML 2**
CT01.08: Legal provisions, regulations and guidelines that require authorization for the **import, export or destruction of investigational medical products (IMPs)**	**2**
CT01.09: There are requirements for monitoring and reporting of **adverse events and reactions during conduct of CT.**	**2**
CT01.10: There are guidelines on the **format and content** of clinical trial applications	**2**
CT01.11: Legal provisions and/or regulations allow the NRA to **recognize and use** relevant clinical trial decisions, reports or information from other NRAs, or from regional and international bodies.	**1**

CT02 Arrangement for effective organization and good governance

CT02.01: There is **a defined structure with clear responsibilities** to conduct clinical trial oversight activities	**ML 2**
CT02.02: Documented procedures are implemented to **ensure the involvement and communication between all stakeholders relevant to CT**	**3**

CT03 Human resources to perform clinical trials oversight activities.

CT03.01: Enough competent staff (education, training, skills and experience) are assigned to perform clinical trials oversight activities.	**ML 3**
CT03.02: Duties, functions and responsibilities of the staff, in charge of CT oversight activities are established and updated in the respective job descriptions	**3**
CT03.03: Training plan developed, implemented and updated at least once a year	**3**
CT03.04: the NRA performs and maintains records of staff training activities	**3**

CT04 Procedures established and implemented to perform clinical trials oversight

CT04.01: NRA has access to an advisory committee for review of CT applications and post approval safety and compliance issues.	**ML 4**
CT04.02: The existence of the ethics committees (ECs) with clearly defined composition.	**3**
CT04.03: Non-clinical data is considered within CT application review.	**3**
CT04.04: There are defined roles for ECs at all levels (e.g. national, subnational, or institutional).	**3**
CT04.05: Documented and implemented procedures exist to review CT applications	**3**
CT04.06: There are procedures for EC responsibility for clearance and follow up until completion of the clinical trial	**3**
CT04.07: The same policies are used for the evaluation of CT applications regardless of the applicant (e.g. domestic, foreign, public sector, orprivate sector)	**3**

CT05 Mechanism exists to promote transparency, accountability and communication

CT05.01: There is clarity about the funding of the ethics committee and its members	**ML 3**
CT05.02: The list of the clinical trials (approved and rejected applications), including summarized evaluation reports by the NRA, are publicly available or recorded in a domestic or international database	**4**

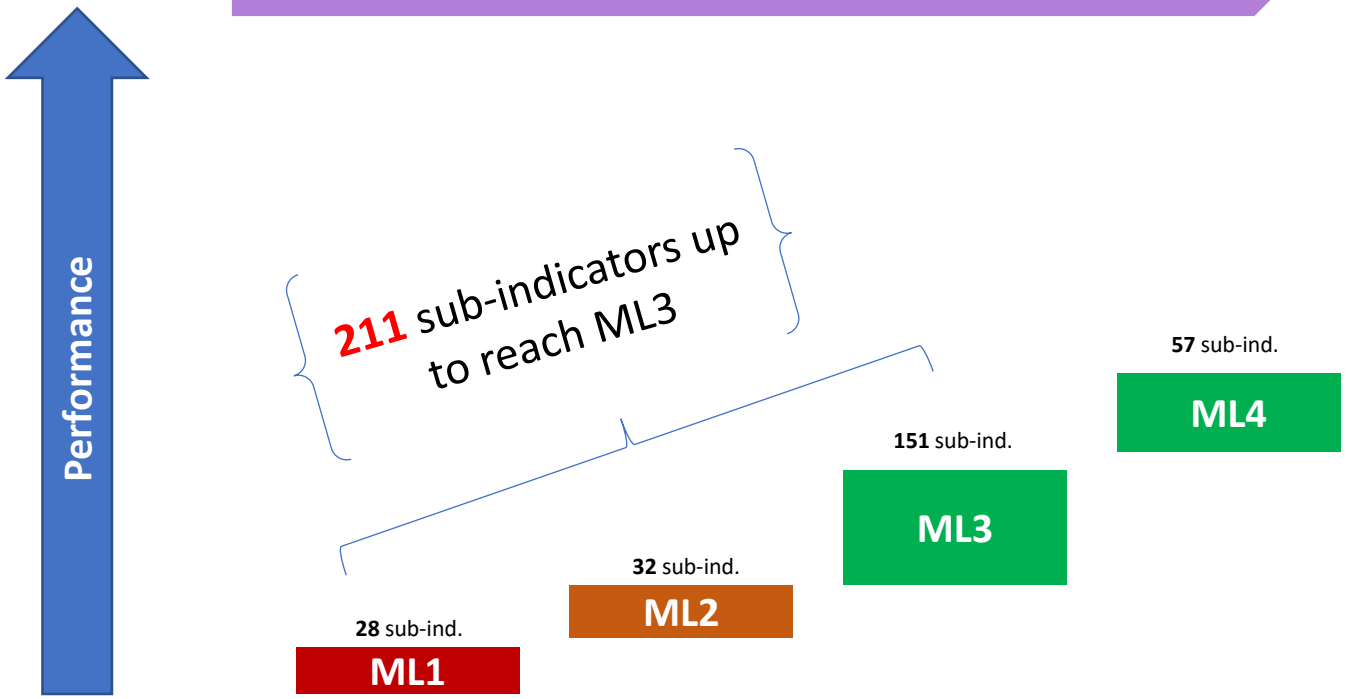
CT06 Mechanism in place to monitor regulatory performance and output

CT06.01: There is **an internal list or database** of **all approved and rejected CTs**, and the NRA maintains a record of each approved and rejected CT	**ML 3**
CT06.02: **Performance indicators** for the clinical trial oversight activities are established and implemented	**4**
CT06.03: **Progress report** from sponsors or clinical research organizations (CROs) during and after clinical trials sent to and shared between NRAs and ethics committees.	**3**
CT06.04: There are **timelines for the assessment of CT applications and an internal tracking system t**o follow the targeted time frames	**3**

Indicators and Tools for WLA CTO Performance Evaluation

NRA-ML & WLA: What's being measured?

NRA Maturity Defined by Benchmarking using GBT



How well a regulatory system is configured?

WHO Listed Authority Defined by PE Indicators and Tools

WLA

- **56 indicators**
  - ❑ **36**/57 of **ML4 indicators**
  - ❑ **20 PE indicators**
- **5 PE Audit Tools**
  - ➢ MAA expert review
  - ➢ VL field visit
  - ➢ RI-GMP & **GCP observed audit**
  - ➢ LTA expert review
  - ➢ **CTAA expert review**

How well a regulatory system operate?

ML: maturity level; **PE:** performance evaluation; **MA:** registration & marketing authorization; **VL:** vigilance; **RI**: regulatory inspections; **LT:** laboratory testing; **CT:** clinical trial oversight; AAR: application assessment report

Source: WHO RSS

Components of the Standard PE process

I - Audit against indicators*			II - Evaluation of selected regulatory functions using PE tools	
Regulatory system and functions	Mandatory ML4 sub-indicators**	PE indicators		
Regulatory system	14	4	not applicable	Cross-cutting
Registration and marketing authorization	3	3	Expert review of MA application assessment reports Off-site evaluation	
Vigilance	4	7	Vigilance field visit On-site evaluation	
Market surveillance and control	2	2	not applicable	
Licensing establishments	2	-	not applicable	
Regulatory inspection	5	-	Good manufacturing practices/ good clinical practices observed audit On-site evaluation	GCP-OA
Laboratory testing	3	1	Expert review of laboratory activities On-site evaluation	
Clinical trials oversight	2	3	Expert review of clinical trial application assessment reports Off-site evaluation	CTAAR Expert Review
RA lot release (vaccines)	1	-	not applicable	
TOTAL	36	20		

* Desktop audit, with provision for onsite evaluation.
** May also include a review of relevant ML3 sub-indicators that were not fully implemented when assigning an overall ML3 rating (see also .7.1.2 below).

Source: Operational guidance for evaluating and publicly designating regulatory authorities as WHO-listed authorities.

Mandatory ML4 GBT sub-indicators for clinical trials oversight

WLAs for clinical trials oversight must fully implement the following ML4 indicators, as defined in the GBT:

- **CT04.01** RA has access to an advisory committee for review of clinical trial applications and post- approval safety and compliance issues.
- **CT06.02** Performance indicators for clinical trial oversight activities are established and implemented.

Source: WHO manual for performance evaluation of regulatory authorities seeking designation as WHO-listed authorities

PE indicators for clinical trials oversight

- **PE.CT.01** The RA **consistently complies with the timelines** established in its guidelines and SOPs for assessing clinical trial applications.
- **PE.CT.02 The list of clinical trial applications**, including their current status, is **publicly available** or **recorded in a domestic or international database**.
- **PE.CT.03** The RA provides **regulatory support to clinical researchers and sponsors** to assist in the development of new therapies for patients.

Source: WHO manual for performance evaluation of regulatory authorities seeking designation as WHO-listed authorities

Cross-cutting: Regulatory System PE Indicators

- **PE.RS.01** The RA participates in the **WHO certification scheme** on the quality of pharmaceutical products moving in international commerce and issue certificate of pharmaceutical product.
- **PE.RS.02** The RA has established an effective **competency framework**.
- **PE.RS.03** The RA has implemented measures to monitor, evaluate and sustain **the performance of the quality management system (QMS)**.
- **PE.RS.04** The RA has **a mechanism**, supported by adequate regulations, guidelines and/or standard operating procedures (SOPs), **for sharing technical information or any other non-public information about its regulatory decisions, with other authorities**.

Source: WHO manual for performance evaluation of regulatory authorities seeking designation as WHO-listed authorities

Expert review of clinical trial application (CTA) assessments: Evaluation Criteria

- 1-Application Process (including pre-submission procedures, assessment, compliance with regulatory requirements and policies, and interactions with stakeholders)
- 2-Assessment report
  - 2.1-Quality of the report
  - 2.2-Completeness of the report
  - 2.3- Scientific rigour
  - 2.4- Assessment Outcomes & Decision-making
- 3- Assessment follow-up

Source: WHO manual for performance evaluation of regulatory authorities seeking designation as WHO-listed authorities. Annex 2

GxP observed audit for assessing the performance of the regulatory inspection function

Evaluation Criteria

- 1-Inspection preparation
- 2-Inspection conduct
- 3-Inspection reporting
- 4-Inspectors' technical competency
- 5-Inspectors' attitude and skills

Source: WHO manual for performance evaluation of regulatory authorities seeking designation as WHO-listed authorities. Annex 4

Key Takeaways

GBT indicators and sub-indicators provide a structured framework for assessing the maturity and performance of NRAs in CTO. This helps countries identify strengths and gaps in their regulatory systems.

Clinical Trials Oversight is essential for protecting participant rights, safety, and well-being, ensuring data integrity, and maintaining public trust in medical research.

WHO Listed Authority status is a mark of regulatory excellence, signifying that an NRA meets internationally recognized standards for oversight and performance evaluation.

Performance evaluation for WLA designation uses specific indicators and audit tools, including expert reviews, field visits, and assessment of regulatory functions, to ensure robust and transparent regulatory practices.

Continuous improvement and capacity building are vital, as NRAs must overcome challenges such as resource limitations and system complexity to achieve higher maturity levels and WLA recognition.

Collaboration and stakeholder engagement strengthen regulatory systems, supporting effective oversight and preparedness for public health emergencies.

Reference Resources

- Global Benchmarking Tool (GBT) https://apps.who.int/iris/handle/10665/341243
- WHO Listed Authorities (WLA) initiative https://www.who.int/initiatives/who-listed-authority-reg-authorities
- WHO operational guidance for evaluating and publicly designating regulatory authorities as WHO-listed authorities
- WHO manual for performance evaluation of regulatory authorities seeking designation as WHO-listed authorities. Annex 4

Contact to the speaker for questions and feedback

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