A Primer for Clinical Assessors within African Regulatory Agencies

Project Summary and Report

A structured education and training programme for professionals working for government health product regulatory agencies in Africa

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Executive Summary

Regulatory agencies on the African continent are beset by critical skill shortages caused in part by lack of resources and training. While some of these issues are being addressed by the regulatory agencies themselves, there exists an urgent need for targeted training for clinical assessors across Africa. By leveraging robust technology platforms and a network of engaged subject matter experts, Pharmacometrics Africa and its partners led the second iteration of its course "A Primer for Clinical Assessors within African Regulatory Agencies".

Over 12 weeks, this course gave participants an intense deep dive of the core competencies that clinical assessors working in Africa regulatory agencies require to function effectively. To support this goal, international and regional subject matter experts were invited to not only teach their lessons in a weekly live tutorial, but also to further develop a reusable online curriculum and set of resources for use both during and after the course. Placing special emphasis on the interactions between the Regulator and the Regulated, the curriculum was broken into three sections: Construction (building a regulatory dossier), Deconstruction (regulatory assessment of the dossier) and Reconstruction (dossier support of the Marketing Authorization and Product Information for prescribers and patients). The faculty included several graduates from the pilot program thereby demonstrating a valuable "train-the-trainer" aspect of the course tactics.

By the end of the 12-week course, students participated in:

- Over 24 hours of live instruction with lesson leaders and subject matter experts
- 96 hours of online coursework, supported by a broad library of resources
- Group work exercises to critically appraise case studies of completed dossiers on selected topics of relevance to African regulators

A total of 45 regulators were nominated from five participating regulatory agencies – Ghana Food and Drugs Authority (Ghana FDA), Kenya's Pharmacy and Poisons Board (PPB), Nigeria's National Agency for Food and Drug Administration and Control (NAFDAC), South African Health Products Regulatory Authority (SAHPRA), Tanzania's Medicines and Medical Devices Authority (TMDA) and the Medicines Control Authority of Zimbabwe (MCAZ). The University of Witwatersrand awarded certificates of competence in a graduation ceremony to the 24 participants who fulfilled the pre-specified course criteria for this intense program. These criteria were based on their: (i) lesson attendance, (ii) completion of course tasks (iii) group exercise and (iv) examination results.

A detailed monitoring and evaluation (M&E) framework, originally developed as part of the pilot course was also used in this program and addressed data collection time frames, data sources and related risks/assumptions. There were 5 groups of M&E indicators defined at the output level assessing course attendance, completion of tasks and group assignments and implementation of knowledge gained that had been fine-tuned to capture data related to individual participants' objectives. The end-of-course survey had a 39% response rate and revealed valuable evidence of attainment of the M&E indicators together with ideas for improvements to the program.

This document summarizes the efforts undertaken by all stakeholders and students and includes journalistic-style weekly summaries of the lessons that provide deeper insights into content delivery and student engagement over the course.

Background

Adequate clinical trial design and conduct are the basis for patient protection and data integrity in support of a marketing authorization application that is assessed by drug regulatory authorities. The content and structure of the curriculum was created to support each participant in broadening and honing their knowledge of this multifaceted discipline.
To this end, the objectives of this course were as follows:

- Understand how clinical safety and efficacy data are generated
- Appreciate clinical trial design for the various phases of clinical studies
- Appraise different types of clinical data (clinician or observer reported outcomes, patient reported outcomes, laboratory data, instrument measurements) and appropriate validation requirements and procedures
- Recognize the difference between clinical and statistical significance
- Describe how clinical safety and efficacy data may impact on Product Information (SmPC, Package Leaflet, labelling)

The overall aim of the broader programme is to provide a comprehensive knowledge and understanding of the regulatory rules and requirements applicable to the regulatory review of medicines, medical devices and diagnostics, and the capabilities to apply them in work practice.

These objectives were piloted during the first iteration of the course which commenced in 2021, which saw 30 out of 39 participants graduate the course with certificates based on evaluations that included live tutorial and coursework participation, group work and a final examination.

In this second iteration, the curriculum was updated and expanded based on feedback from faculty and staff, with special emphasis placed on student interaction during the live tutorials. This helped to overcome some of the challenges of education using video conferencing. In addition, the group work exercises were revised to add more focus on real-world applications of the curriculum, and allocation of participants in the groups within agencies. The continued introduction of some agency-related faculty in the course and the use of pre-submitted video presentations for assessment of group work were also directly related to feedback from the first course.

Methods

Course structure, content and delivery

The original course structure was proposed based on the outputs from a meeting of experts in June 2020[1] and subsequently further elaborated in a paper by Semete-Makokotlela et al in 2021[2]. For the current program, this curriculum underwent several iterations of review by key participants from the original course as well as participants in the pilot program. A Steering Committee composed of members of the management teams from the agencies involved in the pilot and several international subject matter experts oversaw the process of implementation. Daily operations were delegated to a small core team.

The syllabus included generation of clinical safety and efficacy data, clinical trial organization, roles, origins and types of clinical data, validation requirements and procedures, clinical and statistical significance, and the impact of clinical safety and efficacy data on Product Information. The course was presented in collaboration with academics from local Universities, international institutions and Regulatory Agencies, and was accredited by the University of Witwatersrand, Johannesburg. Impact and sustainability were assessed by a structured independent monitoring and evaluation process.

An online learning platform (Moodle) was used to provide teaching materials. Furthermore, teaching involved a weekly LIVE contact session (2 hours) with faculty and guest lecturers. In this second iteration of the course, the faulty strived to increase discussion and contributions based on the experiences from this class of practicing regulators.

The program was complemented by group work which was integrated in the weekly sessions. Participants worked in small groups comprising members of the same agency to allow maximum opportunities to interact within the group. The aim of the group work exercises were to prepare Regulatory Assessment Reports (RARs) for selected pharmaceutical products including biosimilars, and to compare and contrast the different RARs, including comparisons between African and International RARs for the same product.

The online component of the coursework was integrated on Moodle which allowed monitoring of student engagement, interactive content, group work interactions, live tutorial videos on-demand and assessments. The platform also makes it possible for continuous improvements to the curriculum during the course, based on discussions in the weekly live tutorials.

Faculty

Faculty were nominated by members of the Steering Committee, and then worked with the core team to structure their lessons into self-study materials, self- assessment quizzes, and tutorial sessions. Delivery of the course was done by the lesson leader, co-leader and guest faculty. Each lesson for both iterations of the course have been recorded and are included in the content for each lesson, allowing students to benefit from previous courses - and enabling returning faculty to easily refine their tutorials further.

[1] https://www.sahpra.org.za/wp-content/uploads/2020/10/The-Innovation-meeting-report-30-June-2020.pdf
[2] Semete-Makokotlela B, Mahlangu G, Mukanga D, et al. Needs-driven talent and competency development for the next generation of regulatory scientists in Africa. Br J Clin Pharmacol. 2021 https://doi.org/10.1111/bcp.15020

Participants

Expanding from the previous pilot course, clinical assessors from the regulatory agencies in Kenya, Nigeria and Tanzania were invited to benefit from this program. Participants in the program were nominated by their agency management teams, and were then invited to submit a motivation letter that included at least 3 professional development objectives.

Monitoring and Evaluation

A Monitoring and Evaluation (M&E) framework that was developed as part of the pilot course conducted in 2021 was used again for this course. The LogFramework included M&E indicators, data collection time frames, data sources and related risks/assumptions. In total, five indicators were defined at the output level (monitoring). Objectives related to implementation of knowledge gained in this course were defined by the target group (course participants and their supervisors) and documented prior to the start of the course (baseline analysis). The M&E indicators as well as the end-of-course and evaluation survey were fine-tuned to capture data related to participants' objectives.

Baseline data was collected as part of a baseline survey with further evaluation surveys designed in a way that asked open questions where participants could flexibly describe examples of knowledge implementation post-course. End-of-course survey was conducted after all course activities were completed.

Monitoring objectives

- Collect evidence regarding pilot course participants' engagement in the course (lesson attendance, completion of tasks)
- Collect feedback from course participants regarding the appropriateness of the course: (i) in the context of their daily needs at work as clinical assessors: (ii) to achieve performance-related objectives defined prior course, (iii) appropriateness of the learning format, general structure and organisation of the course
- Consolidate lessons learned/recommendations as a basis for fine-tuning of follow-up intervention(s)

Evaluation objectives

- Collect feedback from course participants regarding achievement their objectives (outcomes) related to implementation of knowledge gained in the curse at 3, 6 and 12 months post-course
- Collect feedback from course participants regarding barriers and enablers of knowledge implementation
- Consolidate lessons learned/recommendations as a basis for fine-tuning of follow-up intervention(s)

Results

Course Faculty

Table 1: Faculty Members and their roles

Name	Role
Arnold G. Vulto	Group Study Co-Lead: Case studies on Bioavailability, Bioequivalence and Biosimilars (focus on biosimilars)
Liese Barbier	Group Study Co-Lead: Case studies on Bioavailability, Bioequivalence and Biosimilars (focus on biosimilars)
Luther Gwaza	Group Study Lead: Case studies on Bioavailability, Bioequivalence and Biosimilars (focus on small molecules)
Memela Makiwane	Lesson 1 Leader: 'Molecule to Market - Overview of Drug Discovery & Development'.
Birka Lehmann	Lesson 2 Leader: 'Clinical Data for Regulation and Product Licensing'
Sunaina Indermunn	Lesson 3 Leader: 'Collection of Clinical Data – What and How'.
Kennedy Otwombe	Lesson 4 Leader: 'Interpretation and Reporting of Clinical Data'.
Elimika Pfuma Fletcher	Lesson 5 Leader: 'Regulatory Assessment of Relevance of Clinical Data for Indication, Licence and Label'
Eric Karikari-Boateng	Lesson 6 Leader: 'Assessment of Validity and Acceptability of Clinical Data for Regulation' Guest speaker: Lessons 2, 8 & 9
Phumla Sinxadi	Lesson 7 Leader: 'Clinical data, Clinical Endpoints and Outcomes'
Sam Salek	Lesson 8 Leader: 'Critical Review of Clinical Data for Efficacy and Safety'
Alan Boyd	Lesson 9 Co-leader: 'Clinical Data: Safety, Risk Management and Mitigation'.
Leander Fontaine	Lesson 10 Leader: 'Marketing Authorisation and Product Information'
Ingrid Klingmann	Lesson 11 Leader: 'Clinical Data for Regulatory Communications'
Shabir Banoo	Lesson 12 Leader: 'Regulators and Sponsors as Partners for Patient Benefit'
John Woodland	Guest Speaker (Lesson #1)
Phumla Sinxadi	Guest Speaker (Lesson #1)
Stuart Walker	Guest Speaker (Lesson #5)

Name	Role
Villyen Motaze	Guest Speaker (Lesson #5)
Adah Adede Allotey-Pappoe	Guest Speaker (Lesson #6)
Maphutheho Selikane	Guest Speaker (Lesson #7)
Ntombi Mthembu	Guest Speaker (Lesson #7)
Saad Shakir	Guest Speaker (Lesson #8)
Villyen Motaze	Guest Speaker (Lesson #8)
Margareth Ndomondo-Sigonda	Guest Speaker (Lesson #9)
Regine Lehnert	Guest lecturer: (Lesson #10)
Doug McNair	Guest Speaker (Lesson #12)
Stephanie De Rapper	Liaison to University of Witwatersrand
Ivana Škrnjug-Yudov	Monitoring and Evaluation Expert
Colin Pillai	Core Team / Scientific Advisor, Steering Committee
Peter Stonier	Core Team / Scientific Advisor, Steering Committee Lesson 9 Co-leader: 'Clinical Data: Safety, Risk Management and Mitigation'.
Bernd Rosenkranz	Core Team / Scientific Advisor, Steering Committee
Faith Kiyuka	Course Administrator
Gabriel McClelland	Content Administrator, IT Specialist

Graduating Students

Table 2: Graduating Students and their respective Regulatory Agencies

First Name	Second Name	Agency
Alexander	Derizie	Ghana FDA
Ali	Arale	Kenya PPB
Asia	Maluleke	South Africa SAHPRA
Benson	Kanji	Kenya PPB
Busisiwe	Mosane	South Africa SAHPRA
Devanisha	Doraswami	South Africa SAHPRA
Ebenzer	Minlah	South Africa SAHPRA
Elsie	Boadu	Ghana FDA
Ernest	Kwame	Ghana FDA
Esmerelda	Janssen	South Africa SAHPRA
James	Gathogo	Kenya PPB
Jennifer	Conduah	Ghana FDA
Maropeng	Rapetsoa	South Africa SAHPRA
Mikal	Ayiro	Kenya PPB
Nora	Obodai	Ghana FDA
Patrick Robert	Ndzovela	South Africa SAHPRA
Pearl	Entsua-Mensah	Ghana FDA
Prevashni	Moodley	South Africa SAHPRA
Samuel	Kerama	Kenya PPB
Sherrit	Molawa	South Africa SAHPRA
Shyamli	Munbodh	South Africa SAHPRA
Siphokazi	Sibisi	South Africa SAHPRA
Steny	Marekera	Zimbabwe MCAZ
Unathi	Mgoqi	South Africa SAHPRA

Course structure, content and delivery

This section of the report presents the objectives for each of the modules, the responsible faculty followed by a narrative summary that focuses on the delivery of the live tutorial. These summaries were shared with the course participants at the end of each week in order to provide continuous feedback as the course proceeded.

Construction

Lesson 0: Regulatory Assessment Case Studies: Welcome to the course!

Faculty: Arnold Vulto, Liese Barbier, Luther Gwaza
Chair: Bernd Rosenkranz

Objectives

- Get familiar with your surroundings
- Expectations and requirements for participation in this course
- Understand the course outline and schedule
- Introduce you to the group assignments
- Get to know each other

Summary

With no fanfare, hype or bunting the 'Primer for Clinical Assessors in African Regulatory Agencies' Course'22 cruised into dock on Thursday 12 September. No longer a pilot but now a real first module in what promises to be a multi module convoy, its first session was already dubbed a bonus (Week 1, Lesson Zero) to the now 13-week program. A bonus as a reward for constructive feedback and critical evaluation of the pilot, adjustments to organisation, licks of paint and refurbishment to the content and Moodle platform, and addition of an academic accreditor and certifier in University of Witwatersrand.

Course'22 has an increase to 46 participants and doubling of Regulatory Agency members with addition of Nigeria, Tanzania, and Kenya to South Africa, Ghana and Zimbabwe of the pilot.

With no time to lose Captain and Chair for the day Bernd Rosenkranz covered the welcome, news, housekeeping and administration with absolute clarity and certainty, leaving no one in doubt of the energy, thrust and direction of the course, time commitment and the complex surrounds of the weekly Lessons. Message to participants: 'Keep up to stay ahead!'.

But, participants note, there was an unspoken message too; that of 'Groups'! Groups are everywhere in Course'22, even though maybe of the same membership – Agency Groups, Project Groups, Breakout Groups, even eventually Mentorship Groups. Groups are there for participants' benefit; to build Confidence, Collaboration, Contribution! Course'22 is not a teaching course; it is an interactive course for learning and experiencing together. Message to participants: 'Participants participate!'.

And so to the content of Lesson Zero. This was a magnificent tour de force of an introduction to the Group Work on critical assessment of clinical dossiers and an essential curtain-raiser to the course, with the Group Work running throughout the course towards presentation and assessment at the end.

Luther Gwaza opened proceedings with a How-to-do-it overview of critical assessment of clinical dossiers in Group case studies of small molecules, logically and neatly packaged and summarised as 'to critically analyse the available information in line with scientific and regulatory

requirements, using risk management principles, to maximise public health outcomes.

Top line, succinct, pointers to the Agency groups to apply relevant skills of communication amongst group members, search and review relevant supporting literature, apply teamwork and collaboration throughout. Remembering Good Review Practices, Risk management and the Links between regulation of medical products and Public Health.

This led to Arnold Vulto and Liese Barbier introducing Biosimilar Medicines - the Regulatory Framework and Clinical Development, respectively.

Biosimilars are highly similar to the reference product, and when developed and licensed are a definite advance for the healthcare system, bringing price reduction through competition, increase in patient access to treatment, providing incentive and budgetary headroom for innovation.

Biosimilars differ from other medicine developments in having distinct regulatory processes and living in an 'upside-down' CTD world of development where comparability studies, not clinical studies, are the cornerstone of biosimilar development. Nevertheless, the aim is all about addressing uncertainty, and clinical studies are needed, but the skill is to know when and what these should be.

Key messages on Biosimilar development were to recognise the different patterns of development (to other medicines), the rigorous and meticulous work required to address the uncertainties inherent in biosimilars (due in part to tertiary and quaternary structures of proteins) and the focus on comparability studies, not de novo proof of efficacy and safety.

All in all, a great and relevant introduction to the Group Work to come on several different molecules/products.

Followed by Breakout Groups, to start the ball rolling on participation, but with too little time left in the 2 hours to complete even the round of introductions……

…..and zeroing in on Lesson '0' overall in comparison to the expectations was that the session went generally well, with the exception of the too short breakout groups. The participants again, like the pilot, did not interact much; there were 2-3 chats and one live question. More engagement is needed! On Agency group connectivity, the Nigerian agency used the wrong (moodle) link to get access and missed the first part, and possibly a similar problem affected the Tanzania contingency; this should be resolved and go better next week (Lesson 1), but a reminder may be needed for the correct link by Wednesday.

The ship leaves dock and the course is set heading to Week 2, Lesson 1 on Thursday 22 September.

Lesson 1: Molecule to Market - Overview of Drug Discovery & Development

Faculty: Memela Makiwane, John Woodland, Phumla Sinxadi
Chair: Bernd Rosenkranz

Objectives

- An overview of the drug discovery and development process
- An assessment of factors that are considered when selecting a clinical candidate
- Discussions on why adequate and appropriate clinical trial design and conduct are needed for patient protection, data integrity and regulatory acceptability

Summary

Yes! The ship has left the harbour and is setting a course, Course'22, for Clinical Assessors within African Regulatory Agencies. Getting up steam from the engine room of drug discovery, the expert crew on the bridge knew well their coordinates for Lesson 1, guided, prompted and timed from the Captain's chair by Bernd Rosenkranz.

Memela Makiwane provided a whistlestop overview of Drug Discovery and Development (let's call it DDD), stopping not for granularity of detail, with audience knowledge assumed from prior learning or from the available pre-recorded lecture, but to focus on taxing questions arising from his conclusion that the drug development process 'is expensive, time-consuming, and often inefficient, with many failures along the way.' A main question relates to the costs and prices of innovative medicines which incorporate the costs of the attritional failures in the DDD pipeline – is it fair for populations who use the medicines to pay for all the failures?

The participants were slow to dive into this headlong but, hang on, with prompting and pointing from Memela, there was soon a very prolific discussion of this complex and touchy subject, with lots of contributions. See, there are no silly questions, no wrong answers. The over-riding opinion, by the way, was that it was justifiable to recoup costs of the DDD process, and this should not be seen as financing failure but as recouping R&D costs to ensure future R&D investment. Thus, maintaining support for the 'R&D – RoI' (return on investment) model of science-driven, independent, competitive, and overall successful, medicines development sector of healthcare and industry. Another positive, also from Memela's conclusion was the continuing efforts being made to refine, revise and reform the DDD process, with emphasis on data-driven approaches, including big data and AI, to gain new treatments, improved patient outcomes and lower costs.

This discussion fuelled the whole of Lesson 1 with lively participant engagement at every opportunity; poll questions, questions on the Chat from participants and faculty, hands raised, and of course in the Break-out group session with some set questions to debate.

Some breakout group logistic challenges stood out: The Break-out groups do not self-start and need some initial prompting; rapporteur to be selected early, questions to be in the rooms from the program and, if band-width and connectivity allows, cameras to be on; have sufficient time for feedback. Break-out groups are a key participant resource in Course'22 - for confidence,

contribution, collaboration – and will be fostered in keeping with the feedback from the pilot course.

The difficult challenge of Lesson 1, and any session, is Time – there's never enough!

Further expert crew John Woodland enlightened the session on his passions for drug discovery in the African continent, with its history of only one medicine in the whole of its pharmacopoeia discovered on the continent. He explained the development of the H3D accredited research centre at University of Cape Town, with its fully integrated drug discovery platform, the first of its kind in Africa. And its vision: to be the leading organisation for integrated DDD on the African continent.

He illustrated his presentation with the DDD of anti-malarial compound MMV390048 (MMV048) bringing to life, in the context of the realities of the scourge of malaria, the rather impenetrable world of laboratories, computers, flow diagrams and Gantt charts.

There were many questions, prompted by John and asked by the participants, which he addressed and they discussed with great interaction in the short time available after his lecture.

Phumla Sinxadi followed with the clinical contribution to the DDD lesson, and ground-breaking it was too. This was on the Phase 1 clinical trial of MMV048, the first clinical step on the route from molecule to marketplace, from bench to bedside, for importance to patients - the first human use of the drug candidate, the innovative medicinal product (IMP), for safety a key moment in translation from non-clinical work including animals to humans, and for Africa the very first First-in-Human (FIH) study conducted on its own African-led drug discovery candidate.

This was a short but thorough introduction to the complex organisation, diligence and care that goes into any clinical trial, and particularly the FIH study with its focus on participant safety, facilities, qualifications of Principal Investigator, training of study team, monitoring measures, calculation of starting dose, study design and conduct, gaining approvals from ethics, regulators, and hospital institution. The watchwords here are safety of trial participants, preparedness for any eventuality, and ability to react appropriately in the interests of those volunteer participants.

The Breakout room discussion had questions on FIH – What should a regulator watch out for in a FIH study? (see above). Should volunteers be compensated for participating in an FIH study? (Yes). What determines the level of compensation? (Inconvenience and expenses, not risk) - which were the most widely addressed in the short time for the Breakout groups, but enthusiastically and eloquently reported by the rapporteurs in the moderated discussion.

All in all a memorable and well-constructed agenda with abundant opportunity for participant interaction, which was taken up with increasing enthusiasm, and augurs well for the rest of the voyage. The good ship Course'22 sails on - towards more Clinical Development in Lesson 2.

Lesson 2: Clinical Data for Regulation and Product Licensing

Faculty: Birka Lehmann, Luther Gwaza
Chair: Colin Pillai

Objectives

- Understand the contents and purpose of the clinical trial application dossier (CTA)
- Understand how sponsor-driven clinical trials meet regulatory needs and expectations
- Understand the contents and purpose of the marketing authorisation dossier
- Understand the elements that make up a clinical program and how this culminates in the SmPC & Product Information (leaflet).
- Appreciate the different roles of clinical data from exploratory vs. confirmatory studies
- Clinical trials in a marketing authorisation dossier
- Preparation of the regulatory submission dossier
- Inspection of clinical trials and their influence on the marketing authorisation
- Understand the link between all of the above and how it relates to the product information that is provided to clinicians and patients

Summary

The sturdy training vessel, 'Course'22', sailed proudly into its second port of call Thursday for its Week 2 Lesson for African regulators' assessment of clinical dossiers. With a dockside Welcome! to his Chair for returning Captain, Colin Pillai, he immediately invited on board Lesson Leader Birka Lehmann for her regulatory expert view of the seascape for this part of the voyage with 'Clinical Data for Regulation and Product Licensing'.

Her lesson was the first to explore the world of Clinical dossiers, initially in their construction, and to illustrate the interactions between sponsor and regulator throughout the medicines' development lifecycle in understanding how sponsor-driven clinical trials meet regulatory needs and expectations.

The detail covered the essential terminology and content for the direction of flow of clinical dossiers, which were outlined in Birka's learning objectives, emphasising: sponsor-led preparation of clinical trial application (CTA) and regulatory submission document (CTD) for Marketing Authorisation (MA) driven by the Target Product Profile (TPP) and the Clinical Development Plan (CDP). This was also a discourse on the interaction with, expectations for and influence of regulators on the product profile throught the structure of CTA and MA submission, through the Common Technical Document (CTD), touching on the regulatory assessment and then the output and outcome in the MA and Product Information.

But, Hey, this was not a teacher-driven litany, but an invitation for the audience to familiarise, refresh and update their understanding of definitions for a sequential order of play in the development of a medicine for key documents such as Clinical Study Reports (CSR), TPPs and CDPs and the inclusion in their data and summaries in the CTD and MA application. And she emphasised the importance and value of interactions of regulator and sponsor through common

understanding of documentary needs and requirements, of meetings, and of inspections and their contribution to the quality of the medicinal product and the continuous improvement of development processes.

Birka could not avoid a broad categorisation of clinical trials designs and phases (more on that at the next port of call), and reference to all these components, activities (and data) contributing to an ongoing integrated Benefit-Risk Assessment and a positive B-R Balance, upon which the MA authorisation decision depends.

This all focuses on the construction of clinical dossiers, but mindful of the later stages of the voyage to come - in regulatory assessment and the output / outcome in terms of Product Information, the Summary of Product Characteristics and Patient Information.

Birka's extensive tour and plan of action for regulatory assessment of clinical dossiers finished with a challenging on board Deck Game, summarising the plan by asking: at each staging point - the Pre-Marketing Authorisation stage (Pre-MA), the MA stage and the Post-MA stage, What tasks are involved? Which data and documents are required? and Who is involved? The session did not have time to play the game in full, because we were preparing to leave port, but it is a fantastic resource for the voyage – please take another look!

This emphasis on interactivity had led to the on-board Breakout rooms, which addressed two questions: Which kind of clinical trials are you (regulators) expecting to see a. for a medicinal product (generic or not) where the presentation was changed from syringe to tablet? And b. for a medicinal product for the addition of an indication?

There were very productive discussions among the groups, who now had their sea-legs, and their volunteer rapporteurs made confident and succinct summaries in the moderated session. Slight issue was that the rooms demonstrated such great variation in their conclusions on the questions, involving every phase of clinical trials and nearly all clinical trial categories and designs – that this indicated that more work needs to be done in the coming sessions to be able to address these sorts of questions; we are at sea, and there is no time for rest and relaxation on this voyage!

However, to emphasise that the rising tide of early and focused contributions from the audience in questions, answers, comments and requests, including Chat converations and Q&A is contributing to expanding discussion and putting material into context as well as revealing gaps and needs – to cross-relate Lessons and the logic of continuity. This was a lively and relevant backdrop for the week's self-learning which from now on takes the audience into a deep dive of course content of clinical assessment for medicines regulation.

This starts next week with the on-board Lesson on 'Collection of Clinical Data, What and How?' So, everyone, prepare your stations staffing the fenders and mooring lines ready for the next port of call for the good ship 'Course'22'.

Lesson 3: Collection of Clinical Data – What and How

Faculty: Sunaina Indermunn, Colin Pillai
Chair: Colin Pillai

Objectives

- Understand the scope of clinical trials in the main phases of clinical drug development.
- Get an overview of how clinical trial data is collected for product regulation, and gain an appreciation of how the clinical trial organisation contributes to the efficiency of the clinical development programme.
- Provide an overview of biological medicines and differences relative to small molecule therapies
- Outline and understand the assessment of bioequivalence and bioavailability.

Summary

Ahoy there! All hands on deck! Came the cry from above as Colin Pillai, once again in the Captain's Chair rallied crew and participants to the cause. This time, in Lesson 3 of the voyage, to emphasise the proximity of one of good ship Course'22's major landmarks - Clinical Trial Island.

For clinical trials, so central to the work of the regulator in assessing clinical dossiers for licensing and product information, were finally within sight by Lesson 3 'Collection of Clinical Data - What and How'.

Landfall was made quickly so as not to lose the opportunity to introduce the first full contribution from The University of The Witwatersrand, Johannesburg in the form of Sunaina Indermun, who led the trek through the circuitous hinterland of Clinical Trial Island with confidence and comprehension.

There were plenty of sights and species of Clinical trials (CTs) to view along the way, including from Lesson 2, many the result of 75 years of evolution from those heady days of the introduction of the mother of them all, the randomised controlled trial (RCT) – of streptomycin in 1946.

Clinical trials, randomised controlled trials, are the core hypothesis-testing experimental tool of medicines development, producing much of the data to form valid and reliable information leading to statements of knowledge of efficacy and safety which in turn are major contributors to the Benefit-Risk assessments and positive B-R balance judgements upon which ethical Product Licensing and Product Information depend.

No clinical trials, No data trails, No trusted treatments!

For this journey Sunaina led the party through the heights of CT Phases I-IV, whose aims were covered in Lesson 2 by Birka Lehmann, but here was the detail of design, data input and expectations for data outcome. Sunaina also took in the swamplands of the CT Protocol in all its glory, a dissection of the big beast into its constituent parts, to discover 'What the trial is assessing and what are the data required to make the assessment?' and, hang on, 'How are data collected in a clinical trial?' Sunaina's presentation allowed Colin to help address a question from the moodle platform [by Prea] as to when Phase1 studies are done in drug development [Answer:

at any time, since PI studies include many clinical pharmacology studies]. This was a testing and arduous trek indeed, but an essential part of the voyage of Course'22.

No regulatory assessor from our six agencies was left behind on the island, all kept up to speed, reminded of the strengths and opportunities of good CT design and conduct. The meeting CHAT continued to be well used with Maropeng politely raising a question about transparency in reporting "…can the investigators publish the study report regardless of what the sponsor decides?..." – to which the able-bodied faculty (Bernd, Colin, Eric and Sunaina) weighed in with responses based on experience and anecdotes.

But in the background they were reminded too of the weaknesses and threats to scientific truth, the crocs lurking beneath the surface of unethical CTs, weak consent, poor design, underpowered execution, hyperbolic interpretation and fabricated publication. Preventable by honesty, transparency, ethical conduct, Good Practices, audits and inspections.

A magnificent tour de force by Sunaina.

En route, up stepped Captain Colin to present a whistle-stop synopsis of the neatest and some would say the most controllable of CTs, the Bioequivalence Study, its conduct, data production, uses and value in crucial places in the clinical development plan and indeed in whole product evaluation (generics).

Back on board, and just before the bio-break, it was to the Breakout Rooms, rapidly becoming renowned as 'Lifeboat Drill', where sink or swim is the order of the day. Today by and large the message in the bottle was that it was a sink day! Despite pre-knowledge of the Breakout question and opportunity to prepare an answer, reinforced by Sunaina's lecture ('Complete sections of the protocol [Safety assessment, Statistics, Ethical & Regulatory aspects, Trial management] from a provided protocol'.) the groups engaged in managed avoidance. One could not agree, select or volunteer a rapporteur, others purported not to know the question, not to have understood it, not to have had time to address it! Lifeboats were not meant to be like this; stuck to the side of the ship!

It's probably all understandable, given the time pressures of the day and multiple activities to do on board Course'22 during the week. Perhaps the participants could suggest what they would like to address / answer in the randomly allocated 20-minute Breakout Groups – please use the Moodle Feedback Forum?

Next week Course'22 Group Work itself will be introduced, following the backgrounders and preparations in Week 0. Also Lesson 4 ' Interpretation and Reporting of Clinical Data'.

Anchors aweigh!

Lesson 4: Interpretation and reporting of clinical data

Faculty: Kennedy Otwombe, Liese Barbier
Chair: Colin Pillai

Objectives

- Understand statistical considerations when clinical data on efficacy and safety are interpreted and reported
  - Understand statistical aspects for review in regulatory submissions
  - Understand the relationship between study hypothesis and efficacy results and how it supports safety
  - Understand intercurrent events and methods used to adjust for them
- Gain an appreciation of how clinical data is constrained by clinical trial design and conduct, and by regulations, guidelines and good practices
  - Understand how data quality impacts efficacy and interpretation in clinical trial design
  - Learn factors that affect interpretation of trial results
  - Understand the effect of study design on treatment effect and interpretation
- Gain an appreciation of the likely impact of Local versus Global clinical data on the regulatory approach to assessment and decision-making

Summary

Course'22 sailing into calmer waters for Lesson 4? After the shock and turbulence of Lessons 1-3 and the apparent non-stop introduction of pile upon pile of materials and requests – pre-recorded, live, documents, group work, questions, posts, assignments in each week's workplan. Becalmed? No! not a bit of it, as hinted before, there is no rest and relaxation on this voyage with its ultrashort 2-hour Thursday live sessions.

Coming to the end of Part 1 of the course – on sponsor-led construction of clinical dossiers for regulatory assessors; a waypoint must be found to tie down the wide content and expectations for detailed self-study, reading and project work from Lessons 1-3 'Molecule to Market: Drug Discovery and Development'; 'Clinical Data for Regulation and Product Licensing'; 'Collection of Clinical Data: What and How' to coordinate and integrate it all to bring context and foster learning from the course for regulatory assessors of clinical data.

And the waypoint marker buoy around which to focus all this was Lesson 4 Lead Kennedy Otwombe, 'Interpretation and Reporting of Clinical Data', emphasising that clinical data and interpretation do not get far without statistical input, not in tests and P-values, but in statistical and scientific thinking as applied to the variable human condition. Leading the way were the expected learning outcomes from the week: To learn the factors that affect the interpretation of clinical trial results. To understand: statistical principles for review in regulatory submissions; relationship between study hypothesis and efficacy results; how data quality impacts efficacy interpretation; effect of study design on treatment effects and interpretation; and tales of the unexpected, the dreaded unplanned intercurrent events and how to adjust for them.

Kennedy delivered these messages and more besides expertly and with aplomb.

Important issues to consider when evaluating and interpreting clinical trial results: Hypothesis testing; Patient population; Data quality; Data analysis, Statistical analysis plan (SAP), Statistical interpretation; Causal inference; Estimands / Intercurrent events. Main sources are ICH E9 (statistical principles for clinical trials) and ICH E9(R1) addendum for Estimands and sensitivity analysis. Do not miss out on referral to the CONSORT Guidelines when reviewing clinical trials.

Throughout Kennedy's tutorial ran the threads of the importance of detail, planning and unwavering scientific approach; applying prospectively in planning and preparation the logic and common sense brought to the many ethical and practical dilemmas of planning, conducting, interpreting, and recording clinical trials and data. When something is unplanned cf. intercurrent events, how much they perturb the system and must be dealt with!

This lesson and its intended follow-through with discussion from the audience was set up to bring coherence to the first section of the course in its aim to show how sponsors go about their business of preparing regulatory submission dossiers for regulatory scrutiny and licensing decisions. If this Course'22 aim was achieved may come in the feedback. Once again the breakout groups did not give much clue or credence to this expectation. Responding to a set pre-read of a clinical trial did not evoke much response as many of the audience had not found time to do the pre-read or address the question(s) in the time available. Is this a message in

the bottle for future breakout group? Faculty, keep the questions simple with no pre-reads; they would still likely stimulate thought and more responses in the given time.

Liese Barbier, guest lecturer and co-coordinator of the Course'22 long-running Group work, re-emerged from Lesson 0 unscathed, and gave another backgrounder in preparation for the Group work (Groups are by regulatory agency) on preparation of regulatory dossiers in response to MA authorisation applications. This backgrounder was on 'Biosimilars: Clinical Resource Material and a Case Study', and for this trastuzumab biosimilars were in the spotlight. And what a megawatt spotlight this was too, certainly deserving of a return to the slides and the lecture outside of the lesson.

Liese gave a phenomenal insight into thinking applied to licensing of biosimilars, with the reverse strategy to small molecules. The emphasis on comparability studies, at the expense where possible of clinical trials, the inversion of the CTD pyramid to focus on the totality of data, as opposed to a multiplicity of trials.

All essential preparatory materials for the Group work to come but very deserving of a revisit to the material and slides during the ensuing weeks to ensure that when it comes to it the regulator can explain in a few slides the rationale for licensing based on the properties and problems that biosimilar medicines could potentially present to the regulator.

Liese left the audience with a challenging case study and facultative exercise to stimulate thinking over the coming weeks, and which were right on the button for the expectations from the Group Work.

Case study: assess and critically discuss the biosimilar data package (including the clinical program) of an assigned biosimilar product in relation to the biosimilar development guidelines:

- Insulin biosimilar (Abasaglar biosimilar, Lantus reference product)

- Infliximab biosimilar (Flixabi biosimilar, Remicade reference product)

Facultative exercise (will be made available on Moodle):

Aim: To train assessment and comparison of the design and results of the comparative efficacy/ safety studies for biosimilar development.

Five fictional trastuzumab biosimilars with varying study designs and results:

- Rank them with #1 being the “strongest”/most convincing clinical package, #5 the “weakest” clinical package;
- Motivate (justify) what your decision would be as a regulator?

Next time, the start of Part 2 of the course, as the regulatory assessors move in on the submitted dossiers: ‘Regulatory assessment of relevance of clinical data for Indication, Licence and Label’ with Elimika Pfuma Fletcher.

Deconstruction

Lesson 5: Regulatory Assessment of Relevance of Clinical Data for Indication, Licence and Label

Faculty: Elimika Pfuma Fletcher, Stuart Walker
Chair: Bernd Rosenkranz

Objectives

- Assess the relevance of clinical data (benefit-risk assessment) to support the therapeutic indication and label
- Evaluate the generalizability of clinical data to support the proposed therapeutic indication and label

Summary

It was all plain sailing on the good ship 'Course'22' this week as the Regulatory Assessors took over the bridge under watchful eye of Captain Bernd at the start of the second part of the voyage and their deconstruction of the Clinical Dossier submitted by the Sponsors in 'Regulatory Assessment of Relevance of Clinical Data for Indication, Licence and Label'.

Lesson Leader Elimika Pfuma Fletcher ushered in the star act of Stuart Walker to regale all on board with his comparative approach to Benefit-Risk Assessment (BRA) of medicines. It was the epitome of good navigation through the structured and logical world of BRA initiatives from FDA's 5-step framework to EMA's 8-step framework PROACT-URL to his own Unified Methodologies for BR Assessment, UMBRA. Far from being the darkest part of a shadow, Stuart's UMBRA was all sweetness and light harmonising the other industry and regulatory frameworks to produce one which steered a true course through BR Assessment to steady all hands as the final judgement call was made on the positive BR Balance, so necessary for the licence and market maintenance. Stuart completed his lecture on the important area of the documentation needed to record the BRA. The publication on UMBRA development (Ref in the L5 materials) suggested that testing the practical application and validity of the UMBRA framework through a prospective study would help to determine its place in global medicines development and assessment; maybe here were opportunities. The sounds of positive progress in an oft neglected area of exactly how BR assessment is conducted, by whom, and with what outcome. Mikal couldn't get enough and thought in the Chat that Stuart should be given more time – far too short for his clear and valued presentation.

Maropeng asked whether costs should be considered as well as Benefit-Risk in assessment of medicines, as most new products are not affordable by patients in African countries. The answer from Stuart, as expected, was that costs are considered but in a 2nd stage review of health technology assessment of clinical and cost effectiveness, often an emotively charged debate, so good to be separated from the primary consideration here of efficacy, safety and quality to meet patients' clinical needs.

The Breakout rooms followed the same tempo, and astonishingly generated a large amount of

discussion, as if there had never been a problem with electing a rapporteur, answering a list of questions, or presenting to the group! All did well, and were duly congratulated.

One question, of course was on BRA framework and 'if your agency doesn't have one what might be the major benefits of adapting a systematic standard approach to BRA?' Not just one opportunity to get frameworks into agencies – but one after the other, they tumbled out. Stuart was pleased to add that SAHPRA was now working to introduce a BRA, where none has existed before. In a prospective study, three reviewers were working with three old products and three new products and it was hoped that UMBRA framework would demonstrate that the 5 key frameworks used by the pharmaceutical industry and regulatory agencies could be consolidated

effectively into a single framework—namely, the UMBRA. He added that if any other agency wanted to do the same, well, here he was to facilitate and troubleshoot, what better offer could be made, so no need to hide in the shadows, talk to your management and step forward today.

The other breakout question on 'What are some opportunity spaces or focus area for your agency in the conduct of clinical data review beyond regulatory reliance (specific indications, type of products etc)?' drew an equally positive and prolific response from its allocated groups. Elimika then stepped in to give a truly fascinating lecture, from her personal opinion, on 'Translating Benefit-Risk review to Support Indication and Label' to provide the examples and granular arguments to back up Stuart's systematic BR assessment framework methodology. A sweeping and detailed review of submitted material but with a simple conclusion that the product indication statement is generally based on overall study population in safety/efficacy trials; from which labelling can further describe benefit-risk considerations for subpopulations. Subpopulations can be evaluated as part of efficacy trials or separate trials (e.g. pregnancy, lactation, organ impairment).

This was another tour de force, which has come to characterise this voyage. The expert lectures and materials are worth revisiting to establish the detail. Both lectures are supported by the homework material and questions which will establish how the submitted clinical data are assessed to be relevant to licensable indication and label.

After this week of practical assessment of the submitted dossier, hopefully the waters will stay calm for the next Lesson 6 with Eric Karikari Boateng from Ghana FDA on 'Assessment of validity and acceptability of clinical data for regulation.'

Lesson 6: Assessment of validity and acceptability of clinical data for regulation

Faculty: Eric Karikari-Boateng, Adah Adede Allotey-Pappoe
Chair: Bernd Rosenkranz

Objectives

- Understand the critical review element of the clinical sections in a regulatory submission, especially as it relates to efficacy and safety.
- Conceptualize how critical review is used in making a regulatory

assessment, decision and recommendation

- Interpret and use validation/qualification requirements and procedures for clinical data in regulatory work
- Analyse the different types of clinical data and assess their validity and significance, including changes made after authorisation, foreign data acceptability and region-specific requirements

Summary

Coming up to the Half Way point in the voyage of Course'22 and Lesson 6, the ship continued its cruise through still waters and all remained calm for the regulatory assessors looking out to sea from the bridge, as the star Pilot was welcomed on board to guide the ship through tricky local waters.

Eric Karikari Boateng, Ghana FDA, assumed his guidance role with the confidence and direction which only comes with real-world experience and a respect for the potentially turbulent waters and a prior knowledge of the destination – for where he wants the ship to dock. This was eminently demonstrated in his extended Lesson 6 discourse on 'Assessment of Validity and Acceptability of Clinical Data for Regulation'.

In this he addressed all the important matters facing regulatory assessors in their scrutiny and assessment of clinical dossiers. Those factors impacting the acceptance of clinical data from USA, Europe and Africa were highlighted. The assessment of the clinical data package itself including foreign clinical data was explained for its fulfilment of regulatory requirements in the new region, Africa. This included assessment of extent of extrapolation possible for the foreign clinical data for the new region.

These main hubs of his lesson and guidance allowed Eric in masterly form to give an indication of those aspects of the clinical dosser which should give reviewers cause for concern and raise their critical antennae for possible pitfalls, minefields and hurdles having implications for smooth and successful assessment of clinical data in the region or locality. Prominent amongst these were population demographics and ethnic factors; the need for bridging studies for efficacy, for safety as well as additional needed studies; PK-PD studies; drug-drug interaction studies; comparators used in clinical trials of different patient subsets; extrapolation of foreign data – the list goes on. Importantly factors making the impact of ethnic factors less likely (lack of metabolism or active excretion, a wide treatment dose range and flat dose-response curve) or more likely (enzyme polymorphisms). Safety data, adverse reactions linked to genetic factors, are a large factor which leads into the issue of possible post-approval changes which need to be thought about – specific emergent safety problems e.g., myocarditis; warnings to add e.g. hydroxyurea and sickle cell crisis; mechanism of action, dose-response curves, inter-subject variation, laboratory tests. This lesson gave a true insight into the vast range of possibilities for critical assessment of the clinical dossier, and the implications for its content validity and acceptability for meeting regulatory requirements of the new region at large, or even country and locality.

Eric, a true star for explaining the application of the practical, experiential, real-world African context for what is relevant, important and has a bearing on licensing, patient safety, and ultimately benefit - risk assessment of medicines. A lesson not to be missed by anyone, and to

be revisited as necessary. But that was not all – the Breakout session focused its question, to all groups, around the theme of

Eric's lecture to tease out the extent of relevant factors to consider in the critical assessment of clinical dossiers 'As the Regulatory Assessor what factors would you look out for requiring critical assessment for fulfilment of the Regulatory Requirements for the New Region?'

The ship's company of regulatory assessors, perhaps you, picked up from last week and addressed this with such great gusto, extending even Eric's examples from his lesson, such that the boat was itself beginning to list, but fortunately not capsize.

Certainly, this was a prolific breakout session, which contributed greatly to the plenary discussion afterwards, amalgamating all the lists of factors under the guiding hand of our ship's Pilot Eric Karikari Boateng.

As a bonus we found a stowaway on board, a student from last year, Adah Allotey-Pappoe, from Ghana FDA, who gave feedback on her experience of the course and how it had helped her in her practical work. She also contributed to the Breakout session this time - what great endorsements.

To repeat, the Voyage of Course'22 is Halfway there! Congratulations and well done to all our fellow travellers, pilots, captains and stowaways!

Lesson 7: Clinical Data: Clinical Endpoints and Outcomes

Faculty: Phumla Sinxadi, Ntombi Mthembu, Maphutheho Selikane
Chair: Bernd Rosenkranz

Objectives

- Have an understanding of the definition and the conceptual framework of end-points, surrogates and biomarkers
- Assessing the relevance of clinical data to the therapeutic indication and proposed label applied for in the regulatory submission
- Assess the relevance of clinical data to the therapeutic indication for patient-focused drug development: Patient reported outcomes in regulatory submissions
- Be aware of global initiatives to establish a framework for concurrent submission and review among international partners.

Summary

Just when you thought the voyage was half-way over and it was plain sailing all the way home, the clouds gathered, waters became choppy, and the horizon narrowed for Course'22 as Lesson 7 got under way and focused in the most complex and challenging topic to date with its consideration of 'Clinical Data: Clinical Endpoints and Outcomes.'

For here the regulatory assessor, seeking truth about product efficacy and safety from deconstruction and review of the clinical dossier, would find a host of innocent looking objects which could easily undermine and destabilise the ship. Whilst well-defined clinical endpoints are

the key to the value of clinical trials in determining

absolute and comparative efficacy and safety of an intervention, their substitution by surrogate endpoints, some derived from biomarkers, and composite endpoints could easily spoil the party.

Introduced for very positive reasons to foreshorten clinical trials when the clinical outcome is variable and prolonged, to make trials more efficient in terms of participants, time and costs could all be reversed by poor definition, selection and lack of validation of the surrogate or composite endpoint, not to mention the issue of a false benefit-risk evaluation, through the shorter trial failing to reveal the delayed or long-term harm / adverse reaction of the new medicine.

All of these and more examples from an elaborate SWOT analysis of surrogacy was expertly unravelled and explained by Lesson leader Phumla Sinxadi. Her enthusiasm and mastery of the subject led to an equally fervent response from the audience who revelled in questions and answers which contributed so much to the undoubted success of Lesson 7 to stimulate thought and interest and evoke the regulators' responses based on their own work and agency experience. Validation of surrogates, as for biomarkers and composite endpoints, was the afternoon's key word to gain the trust of the regulators!

This was repeated through a consideration of Patient Reported Outcomes (PROs), another important potential component of the clinical dossier, this time to get closer to a true expression of the impact of an intervention on the patient in understanding, experiencing, and managing their condition / disease. Again, gaining the trust of the regulatory assessor through validation, reliability, and relevance to their assessment of true efficacy and safety is key to the adoption and broader use of PROs and real-world evidence in regulatory submissions.

The enthusiasm of the afternoon was carried on into the breakout rooms, which hardly needed priming to get the discussion going. Here Phumla was joined by two former students from the first course, Maputhelo Selikane and Ntombi Mthembu, and by Bernd to nudge and prompt the discussion. The breakout questions are well worth repeating here as they go to the heart of the live session's intent to stimulate further thought and use of Lesson 7's materials: 'Discuss an example of a biomarker or a surrogate endpoint, if possible from a regulatory submission package with which you have been involved. Which role can/did this clinical endpoint play in the submission?' Same question asked for the Patient Reported Outcomes.

The breakout discussions were the liveliest and best so far in the course and prompted a good plenary summation from the group's rapporteurs and Lesson lead and guests Phumla, Maputhelo and Ntombi.

Maputhelo and Ntombi went on in their presentation to describe the African continent's 'MMV' product clinical studies and their biomarkers.

Clouds and choppy waters of a complex and tricky subject area may be, but the combination of audience, lesson lead and involvement of past course participants, expertly watched over by Captain Bernd made Lesson 7 a memorable session indeed. To add to Lessons 5 and 6, and to prepare for Lesson 8 next week: 'Critical Review of Clinical Data for Efficacy and Safety' all at the heart of the regulatory assessors' review of clinical dossiers. Ensure you get to it, but don't run on the deck; hold on to the taffrail!

Lesson 8: Critical Review of Clinical Data for Efficacy and Safety

Faculty: Sam Salek, Kennedy Otwombe, Villyen Motaze, Saad Shakir
Chair: Bernd Rosenkranz

Objectives

- Understand the processes involved during critical review of the scientific literature, and appreciate how to apply the same principles during regulatory review
- Distinguish clinical significance from statistical significance
- To have an understanding and gain insights into how different tools for grading quality of clinical data are applied

Summary

The voyage of Course'22 continues with more appliance of science for the regulators, and this week a definite visit to the depths of the engine room as the agencies go about their business of assessing the validity and reliability of the clinical data for product licensing on grounds of efficacy, safety and quality.

All this with the expectation of a positive benefit-risk balance for public health, and provision of agreed accurate, reasoned, and comprehensible Product Information for prescribers, health professionals and patients.

But, not so fast, walk before you run! Lesson 8 is the 'Critical review of clinical data for efficacy and safety', which needs some explanation, some toolkits for systematic work, and some practice to achieve meaningful results. The modest learning outcomes of today's session were: Understand the processes involved during critical review of the scientific literature, and appreciate how to apply the same principles during regulatory review; Understand and gain insights into how different tools for grading quality of clinical data are applied. Distinguish clinical significance from statistical significance.

Overseen by Captain Bernd Rosenkranz, this week's panel ably led by Sam Salek with Villyen Motaze and Kennedy Otwombe, expertly led the crew through a hailstorm of tools, processes and procedures descending on the dedicated clinical assessor with weapons enough to get the job done in their forensic assessment of clinical evidence.

Villyen Motaze addressed the principles and practicalities of Evidence Based Practice and the several tools for critically assessing and grading clinical trials (eg. CASP, SIGN, NHLBI). These tools to be distinguished from and not confused with Reporting Checklists (eg. CONSORT, STROBE, PRISMA), but both approaches reminding clinical assessors of the value of commonly applied and systematic approaches and tools in their assessment of submitted evidence.

Critical assessment was reinforced by the logical and statistical thinking of Kennedy Otwombe addressing the Hierarchy of Evidence, which reminded everyone that whilst RCTs topped the list of information coming from the clinical trials, it was systematic reviews and evidence syntheses and clinical guidelines which today sit atop the hierarchy pyramid of evidence.

Evidence Based Practice (EBP) is a systematic approach with 5 'A' steps (Ask, Acquire, Appraise,

Apply, Audit) which provide guidance in accessing, interpreting and applying evidence. In this, statistical significance should be differentiated from clinical significance and the latter applied in practice. This was put in context of the 40-year history and vital importance of EBP's forerunner, EBM, to strengthen the empirical practice of medicine by reinforcing the credibility of research evidence, to understand the results of clinical studies and to determine how best to apply the results in clinical practice.

There have been further improvements in the assessment of hierarchy of evidence, due to limitations of existing hierarchies, importance of processed (filtered) evidence to ensure EBP and the related potential for Guidelines to improve practice and outcomes. A new approach to EBP was proposed in 2004 – the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system. GRADE responds to the credible aspects that improve quality of reporting elements.

The pros and cons of the GRADE system tool were discussed in the breakout groups is it applies to the regulators day-to-day evaluation of submissions made to the agencies – discussing especially Inconsistency (of results from studies), Indirectness (surrogate outcomes, unmatched populations), Imprecision (measure of effect; few studies or events) and Publication bias (not publishing negative results, presenting subsets of data, excluding modifying outcomes of interest); whilst remembering that study limitations too may lead to bias and need for assessment.

See how hot the engine room can get! But the groups measured up to the challenge and produced some of the great discussions of the course. So much so that the panel of Kennedy, Villyen and Sam marvelled and commented at their application and enthusiasm.

After the breakouts, Prof Saad Shakir, from Drug Safety Research Unit, Southampton, UK with a career of regulatory and safety assessment to support him was able to make 'How to read a paper – practical aspects' (aka Critical review of research papers) simple and memorable, with lots of salient examples and anecdotes - the hallmark of experience and wisdom. Not enough time for his complete lecture, but so well worth delving again for his tips for critical review of research publications.

In thanking Sam and the speaker panel of Kennedy, Villyen and Saad, Captain Bernd noted their excellent contributions to the session, raising lively and interesting discussion amongst the crew, alerting these participants to the advantages of a structured approach in regulatory assessment (such as GRADE). By implementing the instruments recommended on board Course'22 during this voyage should certainly help clinical assessors with their continuing and future work as regulators, said Bernd.

This aspect of the course should not be lost, for it refers also to other instruments left as a legacy and for the benefit and use of regulatory assessors and agencies in applying a systematic and structured approach to assessment of clinical data, such as the Benefit-Risk Assessment (BRA) framework, notably Stuart Walker's Unified Methodologies for BRA, the UMBRA framework - and other toolkits and frameworks offered in the weeks to come as the voyage of Course'22 continues to its end.

Reconstruction

Lesson 9: Clinical Data: Safety, Risk Management and Mitigation

Faculty: Peter Stonier, Alan Boyd, Eric Karikari Boateng, Margareth Ndomondo-Sigonda
Chair: Colin Pillai

Objectives

- To understand how clinical data informs the ongoing risk management plan and mitigation of risks of products in development and post-licensing.
- To consider the safety and risk management approaches used in medicines development and post approval
- To consider the safety and risk management approaches used in medicines development and post approval

Summary

Week 9 of the Short Course for African Regulatory Clinical Assessors - starting the home run of the voyage of Good Ship 'Course'22' with the focus for the 4-week finale firmly on the representation of Sponsors clinical data submissions and their regulatory assessment to be presented in the regulatory Assessment Report - and onwards in the Marketing Authorisation and Product Information – for public, professional and patient use.

First off was to give a big Welcome Aboard to Margareth Ndomondo-Sigonda, Head of Health Program of the African Union Development Agency (AUDA-NEPAD) and formerly the first Director General of the Tanzania FDA. An Admiral of the Fleet if ever there was one to inspect Course'22, Margareth's message today was to update on progress with the African Medicines Agency (AMA). Margareth traced the genesis to the African Medicines Regulatory Harmonisation (AMRH) initiative back in 2009 onwards to stitch together the African regulatory system in a stepwise approach to create a platform to work through regional economic communities to improve access to medical products and technologies in Africa. Currently AMRH is reactivating several technical committees that include capacity development to support vaccines manufacturing and operationalising the AMA.

Margareth updated on AMA progress and its value proposition of continent-wide harmonisation of technical standards and processes, aligning with international regulatory standards, coordinating ongoing harmonisation initiatives including joint assessments of medical products, joint inspections of manufacturing sites, safety monitoring of medical products, and current efforts supporting countries to assess complex molecules such as vaccines & facilitate emergency authorisation of products. She updated on AMA's milestone achievements ongoing to the present day.

This was a great contribution by Margareth and was even relevant to the background purpose of 'Course 22', which she complimented very much before departing the ship after her short visit.

One of Margareth's themes - on safety monitoring of medical products - was the topic of today's live session and Course'22 was now at full steam ahead towards 'Clinical Data: Safety, Risk

Management and Mitigation'.

Captain Colin chaired the tightly-scheduled meeting with his usual aplomb. Eric Karikari Boateng and Peter Stonier provided the content. Peter, in the wake of Alan Boyd's Course'21 jet-ski speed presentation 'Safety and Risk Management', focused on the broad sources of safety data and information and their evaluation coming the way of regulators through Sponsor development dossiers, clinical studies, safety and risk mitigation tools and a multiplicity of reports, databases, meetings, committee and working group, and the medical literature.

The messages today were not of the grinding detail of PV case processing and reporting, but of principles of vigilance, diligence and ethical good practices in the interests of patient safety and well-being to which all stakeholders in medicines development must pay attention and indeed homage.

Drug safety vigilance, monitoring and risk management is an ongoing and multidisciplined effort by public and professionals alike, heedless of boundaries such as pre- and post-licensing, important though this is to regulators; truly, a continuous process throughout a product's lifecycle.

Regulators and Sponsors interact on safety and risk on a continuing basis, more than in any other area of medicines development. And today it's not only drug side effects which are the focus, but all areas where medicines can harm or risk harm: medication errors, overdoses, occupational exposure, drug-drug interactions, special situations of pregnancy, extremes of age, misuse and abuse to mention just a few.

Moreover, on the Risk management and mitigation side of the discussion it is the Risk Management Plan presented at the time of Sponsor submissions for licensing which is the bellwether of effective Sponsor-Regulator interaction, stimulating continuous activity pre- and post-licensing, the utilisation of an array of risk minimisation measures and measures of their effectiveness, from routine PV to additional measures, such as enhanced PI, Education (of prescribers - and patients), Controlled access programs, Restrictions to prescribing, and ultimately product availability.

Such enormous collaborative efforts in the historic development of Safety, PV and Risk management and mitigation has moved the field most definitely from 'Crisis Management to Risk Management', and hence the focus today on risk (a word meaning 'probability' but used widely to be synonymous with 'harm').

Benefit-Risk Assessment (BRA) by different stakeholders is a continuous process, and subject increasingly to systematic and harmonised evaluation, as the Course'22 Lesson 5 showed with the adoption of the Universal Methodology for Benefit-Risk Assessment (UMBRA) as an acceptable framework and tool for BRA.

BRA to feed into the judgement of positive Benefit-Risk Balance as the basis for product licensing and maintenance on the market.

Eric brought all this to life with examples, both familiar to regulators present and not so familiar, with his accounts of product safety issues arising pre- and post-marketing and to which regulators had to respond to mitigate harms to an acceptable level (for the patients and their conditions), to license products, and in some cases to refuse the licence. Pyramax, Bedaquiline,

Infliximab, Hydroxyurea were all in his sights, and this was all an illustrative of the vigilance and work that has to happen locally in Africa, to make products effective, safe and suitable for the continent's populations.

Our fantastic crew of regulators responded in style to the provocations of unsafe medicines with the lively contribution to the breakout session, again improving by the week in terms of debate and contributions and active volunteers for the rapporteur role.

Questions this time were on 'Which Post-Authorisation data collection activities to request from the applicant as follow-up on Identified risks and Potential risks found at the Regulatory Assessment of the clinical dossier; discuss their usefulness and give examples for potential outcomes.' And 'What are post-approval Risk Minimisation Measures? Discuss their usefulness and hierarchy.'

What better reminders for the group on the content and implications of this live lesson on the sea of Safety and Risk methods and measures to be contemplated and activated in the Assessment and Follow-up of Clinical Dossier assessment. After all that the session ended just 3-minutes over time, which slightly rattled Captain Colin's Swiss timing, but he did not let it show.

Next week to the true outcome of Regulatory Assessment of Clinical Dossiers, namely, 'Marketing Authorisation and Product Information'. And a focus on Group Work in Course'22.

Lesson 10 Marketing Authorisation and Product Information

Faculty: Leander Fontaine, Regine Lehnert
Chair: Peter Stonier

Objectives

- Understand how the target population for use is delineated
- Understand how decisions are made which events to include as "adverse reactions for the purpose of product information"
- Understand the basic principles of illustrating the frequency of adverse reactions
- Understand how adverse interactions are selected for inclusion in product information
- Understand how to interpret elements of efficacy and safety information in EU and US healthcare professional information
- Understand the types and character of product information provided as part of the WHOPAR

Summary

In Week 10 'Course'22' sails confidently on, with all on board now preparing for the final phase of the voyage and the homecoming.

For clinical dossiers constructed by and with Sponsors early in the cruise and submitted for scrutiny and evaluation by regulatory assessors now comes the production of the Assessment Report and the reconstruction of relevant, valid and veracious information on efficacy, safety and quality to produce the Marketing Authorisation (MA) and Product Information (PI) on therapeutic

indications for the product licensed for use.

With Lesson 10 ‘Marketing Authorisation and Product Information’ comes the opportunity for more networking and linkage of events and sights than experienced so far in the voyage. This is a flotilla meeting with links to the whole family of lessons of Course’22, relevance to the ongoing Group work, and most importantly to the day-to-day work of regulatory assessors themselves, as the final phase brings the journey experiences together to prepare MA and PI and their communication to the world at large.

Perhaps a sudden exposure to the elements of systematic and critical writing with informative phraseology and terminology might bring a rush of blood to the head. How to bring sense to the writing of accurate, evidence-based PI from clinical assessment of benefits and harms? How will the outcome of clinical efficacy and safety evaluation be represented in PI? Indeed, which information must be available or generated to populate PI? How to read and compare clinical evidence in PI? How the resulting PI can bring comprehension, context and caution to a variety of readers and stakeholders from regulator, sponsor, payer, prescriber and patient - regional and local.

Fortunately help was at hand with Lesson leaders Leander Fontaine, a global expert in medicines’ labelling and Product Information and Regine Lehnert, a European regulator with strong links to Africa through PharmTrain and the WHO Prequalification programme.

With calmness and care they steered a path through the sea of data and information to provide a ‘How to do it’ guide to sourcing, collating, assimilating and producing Product Information.

Leander used his long experience in the field to show how, for example US FDA and EU EMA favoured terminology can be interpreted and translated to meet regional and local needs in other parts of the world, and notably here on the continent of Africa. From this he has compiled a magnificent ‘Companion Document’, tailored for more bespoke local use and sectionalised for Efficacy and Safety, and for recognition, interpretation and possible reconciliation of differences between agencies.

Keeping in mind too that Product Information is forever on the move, developing, changeable and responsive to post-authorisation labelling guidelines, best practices, ethical clinical practices and trends in clinical management and treatment. All are addressed in the Companion Document, in sections on writing and reviewing PI, and the section on interpretation of differences which emerged between agencies, how they became visible and confusing for the reader and how they might be resolved.

The Companion Document is a legacy tool for Course’22, a personal compilation, not intended to replace or compete with agency guidances, but of undoubted value as a reference for regulatory assessors to see the possibilities and nuances for local and regional interpretation of PI.

Regine’s presentation put practical meat on the bones of PI by illustrating where PI is sourced, for example from abridged applications for innovator products, novel products based on Reliance, generics and biosimilars; and in general from national treatment guidelines, always mindful of comparability and applicability for the PI of relevance largely to the SmPC, PIL and Labelling. Regine illustrated the decision-making process for selecting relevant PI for the product, the

indication, the local region, and the consideration of many patient-related factors and variables. She referred throughout to examples relevant to the continent, to Reliance and to WHOPAR.

The breakout session showed again the willingness of the now-seasoned voyagers to contribute to a rich discussion, this time on the question in which therapy areas would regulatory assessors expect differences between the uses as per EU/US PI and uses in their own countries; how will this impact what to include and discuss in their local PI; which sections of the local PI may have to differ from EU/US PI. All relevant ongoing questions for thought, consideration and action after Course'22 is over.

The groups in their enthusiasm rightly focused on the predominant local problems and issues in for example the many infectious diseases and oncology, or possible interactions with complementary medicines.

Regine in her plenary summation pointed out that in fact the questions were relevant to All therapy areas, and All content of PI, and that All sections of the SmPC need to be considered. Illustrating again the breadth and depth of PI and its inherent changeability and development, with a need to focus at all times on comparability, applicability, local requirements and the need for constant benefit-risk assessment.

Lessons indeed for regulatory assessment of clinical data and their interpretation and translation to PI in localities and countries on the continent. There is no one-size-fits-all as far as PI is concerned. This is a variable feast, both for initial MA and for post-authorisation changes, always mindful of benefit-risk assessment and its appropriate representation in the PI.

The final link of the day was in preparation for next week's Lesson 11 'Clinical Data for Regulatory Communications' another chance for an overview and linkage of the whole of Course'22. The lesson will present the regulatory communication tools that are used for different stakeholders as part of the MA and post-authorisation, how risk management plans are developed and monitored, and differentiating communications on drug applications made first in Africa from those of medicines already approved elsewhere in the world.

In preparation, regulatory assessors are requested to prepare pre-reading focused around the EPAR.

Meanwhile, Course'22 voyages on and now prepares to re-enter home waters.

Lesson 11 Clinical Data for Regulatory Communications

Faculty: Ingrid Klingmann
Chair: Peter Stonier

Objectives

- Present the regulatory communication tools that are used for different stakeholders e.g. doctors, sponsors, patients as part of the marketing authorisation and post authorisation
- Appreciate how risk management plans are developed and monitored
- Differentiate between communications on drug applications where the application is made in

Africa for the first time and communications on drugs already approved elsewhere in the world

Summary

Course'22 is heading for home waters and the landing ahead has been sighted.

Lesson 11, the penultimate, picks up the review and assessment of clinical data from the construction of 'Marketing Authorisation (MA) and Product Information (PI)' (Lesson 10); this in turn is informed by 'Clinical data; Safety and Risk Management' (Lesson 9) and by 'Critical Review of Clinical data for efficacy and Safety' (Lesson 8).

Lesson 11 thus takes information for MA and PI from the assessment of efficacy, safety and quality from the submitted dossiers with the all-important title 'Clinical Data for Regulatory Communication' addressing matters to do with communication tools for informing public, professionals and patients waiting patiently on land to hear the profile, properties, cautions and contraindications for their newly licensed medicine.

So, with Lesson 11 comes another opportunity for course integration, linking earlier sections on dossier preparation, submission and regulatory assessment to reconstruct the clinical data, as benefits and risks, via strict terminology into the Product Information from the Marketing Authorisation.

Expertly led by Lesson Pilot and Leader Ingrid Klingmann the regulatory communication tools SmPC, PI, EPAR, RMP, DHPC were skillfully defined, dissected and described for their different audiences. Accurate, complete and well-reasoned in all respects, these keynote communication tools form the cornerstone between assessment and information.

They are backed by more informal and these days patient-friendly means of benefit-risk communication. Tools and channels, currently also used by Regulatory Networks internationally for health professionals, prescribers, patients and public: Website and web-based media, Press, Inter-authority communications, Public enquiries, Bulletins and newsletters, Scientific journals, and dare it be said, the Social media. Tales for another day!

But, like all things to do with communication, a many-headed beast from the deep, there is an under-current, a sub-plot, a read-between-the-lines agenda. Here, in the background to Lesson 11, was the Purpose for regulatory communications, the need for users to develop trust in regulators' decisions, through the timely, comprehensive and adapted communications on their decisions to establish confidence and trust in their competence and dedication to the public health. These attributes always need to be refreshed and sustained whenever possible in this ever-changing and oft-fickle world of public expectation, blame culture, and trial by media.

Here was the demonstration of differing regulatory decisions and statements based on the same clinical data – well illustrated in the excellent and lively discussions of the Breakout Groups conducted this time at the start of the live session. The rapporteur feedbacks on the dissection of the Ranolazine EPAR into expression in the sections of the SmPC for Drug Interactions and for Contraindications – reflecting also the pre-reading and homework well completed by the Groups and valued by everyone.

The regulators present were also enlivened in the Chat with too many questions and even debates

to comment on during the live session.

One debate started:

Question. 'For (SmPC) Contraindications, what about pregnancy. lactation and paediatrics?'

Answer. Contraindication only makes sense if there is e.g. clinical cases of damage, information from toxicology studies or a theoretically possible pathophysiological mechanism that could hurt the fetus, embryo or newborn. In all other cases the SmPC and PL will say: "no data or not enough experience available, avoid pregnancy and breast-feeding".

Question. I think pregnancy should be a relative contraindication. Risk vs benefit. If there is an alternative, rather use the alternative as there are no clear data.

Answer. "Relative contraindications" don't exist. Either there are obvious reasons for a Contraindication or information should go under "Warnings and precautions".

Question. Regarding pregnancy and lactation, do we contraindicate in conditions where we have no evidence from study data?

Answer. No, under "Warnings and precautions" it is stated that new data on the effect of the drug under pregnancy conditions are available.

Comment: I really do like the conversation on "pregnancy and lactation". For the label itself, the sponsor would usually want to state something like "no data, manufacturer advises caution,... avoid" until there are clear data. BUT this results in shifting the decision to the clinician and the patient. There is (should) be a move towards gathering the data e.g. asking for specific studies. Prof Catriona Waitt from Kampala is championing this topic from an African perspective. And there are also a few (industry) groups that advocate for data gathering. Take a look at this one www.imi-conception.eu

Answer. This is an interesting topic. More and more chronically ill young women consider or happen to experience a pregnancy. For most drugs we know very well their level of efficacy and risks but as soon as the woman gets pregnant we know hardly anything. There are strong efforts at EU-level to improve the collection of data on drug effects in pregnancy and breastfeeding and to create a reliable dissemination mechanism of available information to women and doctors.

Yes, the foreground and background of this great Lesson 11 on Communication Tools, gave food for much discussion, questions and future enquiry, but time was up, honour was satisfied and there were thanks and cheers all around for a well-coordinated and informative session leading into the home-study period.

Next, on to the Lesson 12 Finale as Course'22 docks. Better reconcile 'Regulators and Sponsors as Partners for Patient Benefit' in Lesson 12 and prepare the way to The Course Group work completion and assessment and other Course'22 voyage assessments and feedback.

Enjoy!

Lesson 12: Regulators and Sponsors as Partners for Patient Benefit

Faculty: Shabir Banoo, Douglas McNair
Chair: Peter Stonier

Objectives

- Understand what drives regulators and sponsors throughout the product life-cycle
- Outline applicable regulatory routes that lead to decisions in the course of product life-cycle management
- Defining and determining regulatory reliance as it applies to cooperation at the agency level
- Understand how regulators are integrating real-world evidence (RWE) in regulatory decision-making
- Explore partnerships for development of capacity in African regulators for emerging technologies and patient engagement

Summary

The good ship Course'22 enters its final port of call, with Lesson 12 "Regulators and Sponsors as Partners for Patient Benefit", a lesson that aims to deliver on its promise to draw together the threads and undercurrents of this course to emphasise that no-one is an island in medicines development.

Do competitive sponsors work in isolation protecting their intellectual property (IP) and developing their secret dossiers for submission to regulatory agencies? Do regulators and regulatory agencies work in isolation and confidentiality to assess the dossiers and deliver their verdicts on positive benefit-risk balance, delivering a marketing authorisation and product information?

Well, 'Yes' in terms of impartiality, objectivity, IP protection, confidentiality, and competitor awareness. But, in isolation – not a bit of it! In the real world of medicines development, there must be a mutual exchange and understanding of the needs, expectations, constraints and boundaries between the regulator and the regulated and of the skills, functions and activities which engage the parties in their work, doing their best together, but separated, for the common good – of patient benefit.

For when things go wrong, differences arise, or time, money and people resources are stretched too far in the high-risk business of medicines development, it is the patient who suffers. Only the human factors binding the parties to a common goal and working through commonly understood and agreed procedures can in the end put this right.

Lesson 12 opened the lid on interaction and collaboration between parties in medicines development and notably the sponsor and the regulator.

Shabir Banoo and Douglas McNair put together the background to "Regulators and Sponsors as partners for patient benefit" and "Supporting Regulators and Sponsors Decision-Making in product development and post-authorisation pharmacovigilance" respectively.

In his own lecture Shabir (Chief Technical Specialist and Head, Pharmaceutical Policy and Programs, Right-to-Care organisation linked to the University of the Witwatersrand) emphasised the respective forces that motivate and drive regulators and sponsors throughout the product lifecycle; he outlined the applicable regulatory routes leading to decisions throughout the lifecycle, and emphasising the importance of regulatory Reliance as a present and even greater future binding force in cooperation and togetherness at the agency level.

Finally raising the matter of how regulators are integrating Real World Evidence (RWE) in regulatory decision-making, emphasised one of today's great catalysts in building cooperative bridges between regulator and sponsor in developing medicines. The other great catalyst today is patient involvement in their healthcare decision-making and increasingly in medicines development itself.

Shabir opened the doors on interaction and communication between sponsor and regulator, between regulatory agencies, and now more and more between patients themselves, regulators and sponsors.

Talk of RWE and Real World Data (RWD) brought in the expertise of Douglas McNair (Deputy Director, Integrated Development, Bill & Melinda Gates Foundation) to emphasise the technical advances needed in dealing with RWD to ensure its validity, reliability and relevance for use in the pre-approval area for regulatory assessment and decision making for licensing of new medicines, but importantly to show the common links via RWD for Sponsor and Regulatory decision-making.

He showed that having common technical terminology, codes and tools was the way forward for fruitful and effective communication between the different disciplines in medicines development, including regulator and sponsor, for decision making.

He emphasised too the development of technical common languages needed for mutual understanding by the regulator and regulated – MedDRA, RWE and the increasing parlance of emerging regulatory science to allow regulation to develop appropriately within the law into areas such as adaptive licensing to bring treatments earlier to patients in need, risk based regulation, participation in PV and risk management across the full pre- and post-licensing lifecycle of the medicine development and maintenance.

These were critical discussion points on patient engagement and increasing involvement, its catalytic value and future, such that this was seen as the pivotal point of development of sponsor-regulator interactions and partnership, as well as the coming of regulatory science to address many aspects of regulatory routes, processes and decision-making for the future.

The Breakout Groups contributed hugely this week to opening the debate on interaction, partnership and communication. The Groups 1 & 2 question "Give examples of interactions in the product lifecycle between sponsors and regulators and what is the impact of this?"

From scientific meetings, the many interactions in the pre-licensing phase, the increasing interactions in the post-licensing phase, the consistent interactions of ongoing safety monitoring, PV and risk management and mitigation activities throughout the product lifecycle, and increasing post-authorisation interactions as a result of adaptive regulation and for example post-authorisation safety and efficacy studies, to audit and inspection, the common ground of benefit-

risk assessment, and the special urgent situations that arise – the greatest example being the acceleration activity of the COVID era for vaccines and medications. A rich contribution indeed.

The Group 3&4 question "When providing advice to sponsors, how can you maintain your impartiality, given that you would eventually need to assess the sponsor's submission dossier?" Plenty of response to this. Group meetings, never alone; have an agenda for the meeting; stick to the guidelines for the advice; use neutral language and formal terminology, have no actual or perceived conflicts of interest. There was a realisation that this was a genuine question and maintaining impartiality a real and active aim for legitimate meetings between sponsor and regulator.

Shabir and Doug summarised the rapporteurs' feedback from the groups and emphasised the importance of recognising and knowing the various ways and means for interactions between sponsor and regulator as the way forward. They also mentioned the many interactions involving agencies themselves, concepts and schemes such as Reliance, patients involvement in their healthcare and in medicines development.

But the common technical parlance was not just to communicate now, but to innovate and move forward on both the sponsor and regulator sides to realise such concepts as adaptive licensing, risk based regulation, evidence-based regulatory science itself, RWD/RWE validity / reliability, PV risk minimisation strategies, unbiased benefit-risk assessment and balance.

Lesson 12 of Course'22 delivered on its promise to draw together all the threads and undercurrents of this 12-week voyage. The aim to demonstrate much of the thinking, and the principles, processes and practices which have been evident throughout on the respective work and interactions of sponsors and regulators in providing and assessing clinical data for regulatory decision-making, licensing and product information – for patient benefit.

Before the regulatory assessors from the six African national agencies left the ship, there was thanks from Captain Colin Pillai and his crew to all those regulatory assessors from the six nations' agencies on Course '22 for their consistent attendance on a weekly basis and their increasing contributions to Q&A, breakout groups, chat-lines and in some cases to presentations. Also thanks to the Lesson leads, guest lecturers, group work leaders and all crew who had steered the Course'22 through its 12-week voyage.

So that was it. For the lessons. But not quite the course, for still to come is the Group work on creating regulatory assessment on products and answering questions for group presentations from the six agency groups on 19th and 26th January'23.

And the final course MCQ examination on 2nd February'23.

Group Work

Faculty: Arnold Vulto, Liese Barbier and Luther Gwaza

The case studies covered topics of relevance to the work of a clinical assessor. The faculty presented 2 worked out examples early in the course to help illustrate how to approach the group work, as well as expectations from the class. Over the course of the program, participants worked in small groups on the cases during the course: 2 x biologic agents and 1 small molecule.

Given that assessment of biosimilars is a relatively new topic for regulators across the world, the course faculty also spent time on introductory lectures and reading materials on this exciting topic that holds promise to increase access to these expensive new therapies.

Objectives

- Apply the knowledge and skills from the course to the real-world case(s)
- Summarize the key information that informs regulatory decisions on safety and efficacy of a medicine
- Critically analyze the available information in-line with scientific and regulatory requirements, incorporating risk management principles to maximise public health outcomes

Description of case studies

Group 1 - Case examples of insulin and infliximab

Discuss in your group the criticality and value of patient trials in establishing biosimilarity between the biosimilar and the originator biological product:

- What is the value of clinical efficacy testing in the overall biosimilarity exercise?
- What is the aim of clinical efficacy testing?
- What are limitations of large patient trials in the context of biosimilar testing? Propose mechanisms to solve these limitations?
- To support your responses to the questions above, quote evidence from the case examples of insulin and infliximab

Group 2 - Case examples of biosimilars Flixabi versus Remicaid

Critically assess dossiers/evidence for the originator product (Remicade) versus the biosimilar (Flixabi) as it relates to human pharmacokinetics, clinical efficacy and adverse effects. Identify a specific indication (e.g. rheumatoid arthritis) and quote clinical trial data and/or evidence from the EPAR during your assessment.

- Please reflect on how you would handle the licensing of the biosimilar in the indications that were licensed for the originator product, Remicade.
- Present a summary as to whether you would grant a positive opinion for your agency or not based on the information available to you.

Group 3 - Case example of Pyramax – Target Product Profile

Using the antimalaria target product profile described by Burrows, J.N., Duparc, S., Gutteridge, W.E. et al. New developments in anti-malarial target candidate and product profiles. Malar J 16, 26 (2017). https://doi.org/10.1186/s12936-016-1675-x, discuss the extent to which the fixed-dose combination of pyronaridine tetraphosphate and artesunate (Pyramax) meets this target product profile.

Your discussion should also include key information about Pyramax and the epidemiology of the disease in African settings and globally.

Group 4 - Case example of Pyramax – WHO list of essential drugs

Review and discuss the scientific basis for including the fixed-dose combination of pyronaridine tetraphosphate and artesunate (Pyramax) in the WHO Model List of Essential Medicines.

- In your discussion, consider the quality of evidence (focus on the relevance of the data to the disease and the African settings/context) of the pivotal safety and efficacy clinical studies.
- Based on this evidence, what would be the recommended regulatory decision for using this product in your setting(s)?

Group 5 – Case example of Pyramax – Benefit risk assessment

Review and discuss the relevance of the benefit-risk assessment done by the European Medicines Agency, and their recommended risk management plan for the fixed-dose combination of pyronaridine tetraphosphate and artesunate (Pyramax) in your local population in Africa.

- What additional changes or requirements (with appropriate justification) would you request the sponsor/applicant to address?
- You should pay attention to the most important safety findings and deficiencies noted by the EMA as well as your group's opinion as well as key findings (or uncertainties) that should be part of the benefit-risk assessment.

Group 6 – Case example of Pyramax – African requirements

Review and discuss the recommended product information from the European Medicines Agency (EMA) for the fixed-dose combination of pyronaridine tetraphosphate and artesunate (Pyramax) in your local African population.

- What additional changes or requirements (with appropriate justification) would you request the sponsor/applicant to address?
- Focus on therapeutic indications, posology and method of administration, contra-indications, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, pharmacodynamic properties, and pharmacokinetic properties.

Summary of the Group Work Presentations

Chair: Colin Pillai

GROUP WORK, AHOY!

And so to Group Work! Tackled over the latter weeks of the voyage of “Primer for Clinical Assessors in African Regulatory Agencies Course ‘22”. The clinical assessors’ groups, assigned to their national Agencies, were set projects that they worked on as teams to challenge and push them through the stormy waters towards home.

Group work projects aimed to compare and contrast the clinical evidence base for a small molecule OR a biosimilar product in terms of their Target Product Profile (TPP), licence, label, intended use and impacts on benefit-risk assessments in the African regional context.

Faculty, expert navigators of stormy waters, Luther Gwaza who presented the small molecule example, Arnold Vulto and Liese Barbier, who together covered the biosimilar example, took time and effort to prepare and present worked examples to illustrate the approach to the group work; as well as their expectations for small groups of 5-6 to work on the three cases during the course, two biologics and one small molecule. Since biosimilar assessment is a relatively new topic for regulators across the world, Arnold and Liese spent more time on introductory lectures and reading materials on this exciting topic which holds such promise on the African continent to increase access to these valued new therapies.

After the introductions and familiarisation, Groups worked on their assigned project. This was to prepare a 20-minute Zoom presentation with whole group participation, an innovation for Course ’22, for faculty and Groups alike. Group presentations to the whole ship’s company of Course ’22 were planned over two sessions in January ’23; the presentations followed by virtual Q&A discussion sessions.

Providing evidence from case examples of Insulin and Infliximab, **GROUP 1** was to discuss the criticality and value of patient trials in establishing biosimilarity between the biosimilar and the originator biological product. What is the aim of efficacy testing and what is its value in the overall biosimilarity exercise? What are limitations of large trials in biosimilar testing, and what mechanisms are proposed by the Group to solve them?

This drew many positive and challenging comments from faculty and course assessors. Here are some comments from the faculty who assessed Group 1. “Discussed most but not all questions posed in the assignment. We missed case examples to substantiate their presentation and make it more practical and applied. The presentation pointed out that the need for and value of comparative efficacy testing in biosimilar development should be done on a product-specific basis, which is accurate, but unfortunately this was not further worked out or explained. The reflection and critical thinking as demonstrated by the group was adequate. “

“Overall, the group made a nice presentation and we appreciated that all group members actively participated. Video medium worked out well (slides + video of presenter) in general, but there were some issues with the continuity of the slides. Some general advice for future presentations; include slide numbers; add references to consulted material on the slides. “

GROUP 3 were challenged to use the antimalaria TPP described by Burrows, J.N. et al. 'New developments in anti-malarial target candidate and product profiles' (Malar J 2017, 16, 26) to discuss the extent to which the fixed-dose combination of pyronaridine tetraphosphate and artesunate (Pyramax) meets this TPP. Discussion to include key information about Pyramax and the epidemiology of the disease in African settings as well as globally.

Some of the assessment comments for Group 3 included the following: "The presentation and response to questions were coherent and understandable. The group participants articulated their thoughts and arguments clearly, with critical thinking and addressing most of the key issues with justification for their viewpoints. The group could have critiqued some aspects that were not fully addressed e.g., on use in pregnant women. TPP specifically mentioned use in vulnerable populations and the group highlighted high disease burden in children and pregnant women due to reduced immunity. The presentation fell short in discussing the Pyramax indications on use in pregnancy. However, the issue was very adequately addressed during Q&A session. "

GROUP 4 set out to review and discuss the scientific basis for including the fixed-dose combination that is Pyramax in the WHO Model List of Essential Medicines (EML). Consider the quality of evidence of the pivotal safety and efficacy clinical studies (focus on the relevance of the data to the disease and the African settings). Based on this evidence, what would be the recommended regulatory decision for using this product in your setting?

Here are some comments from the faculty who assessed Group 4: ".. recording was clear and the presentation logically organised and coherent. The group presented information in their language and expression, that is, synthesised information and original, not copied. The recording and discussion demonstrated well-developed ideas and application of the relevant concepts and principles. The group misunderstood the question and did not refer to the EML. Instead they focused on the EMA decision - which in principle was not a significant flaw, except that essential medicines and EML account for additional considerations to regulatory decisions. The slides and recording were clear and well organised; and specific to the question. Although one person did the recording, all the group members present during the Q&A session contributed adequately."

GROUP 5 were assigned the group project of reviewing and discussing the relevance of the Benefit-Risk Assessment made by the European Medicines Agency, and their recommended Risk Management Plan for the fixed-dose combination, Pyramax, in their local population in Africa. What justified additional changes or requirements would you request the sponsor/applicant to address? You should pay attention to the most important safety findings and deficiencies noted by the EMA and your Group's opinion, as well as key findings or uncertainties that should be part of the Benefit-Risk Assessment.

Faculty comments for Group 5. "Professional logical presentation of the scientific data and regulatory procedures (EMA). Use of appropriate terminology. Course materials were not specifically referenced. There was a clear description of the information relevant for the questions posed to the group, including EMA procedures and information from assessment reports, such as Benefit-Risk (BR) information, PK, Drug-Drug interactions, clinical studies. Local issues relevant for the African region were discussed. On this basis, deficiencies and uncertainties, additional possible requirements and BR considerations were presented. This part of the presentation

went well beyond an overview presentation of available evidence and shows excellent insight in regulatory decision making. The points raised in these last slides could form a good basis for the discussion in the Q&A virtual session. The flow of the presentation was excellent, and all group members contributed to the presentation equally which was notable. “

And that was it! The Group presentations for assessment. But where were **Group 2 and Group 6**? No shows for the presentations. Were they lost at sea? Had they taken Course ’22 ‘cruising’ literally and disappeared across the horizon. For sure, they were certainly not sailing on the home straight and towards port. Perhaps they were just exhausted and out of steam?

Four out of the six groups who arrived in Port were far from exhausted, and gave a good account of themselves in their presentations and virtual Q&A discussions of their Group work. Presentations were made by a dedicated representative or by all team members, which was the preferred option. All presenters were well prepared and demonstrated an excellent understanding of the topics. Presentations were concise, to the point and on time, addressing the issues asked in the questions which had been passed to the team. Special attention was given to the regulatory selection in the African setting when data are often lacking for the patient population.

The Group Work project could thus be classed as one of the great successes of Course ’22, providing groups the opportunity for analysis and integration of product data and for continuing learning and development, including decision-making and teamwork, so much part of their daily practice as regulatory clinical assessors.

For Course ’22 the group work project showed massive learning and improvement from the pilot experience in Course ’21. In the end much of this was down to the expertise and application of expert faculty, Arnold Vulto, Luther Gwaza, Liese Barbier to whom everyone owes enormous thanks for their detailed preparation of relevant and exciting product cases, their guidance in project conduct and timeliness, and the subtle management of the whole group work project from beginning to end, including its relevant mapping to the content of Course ’22 sailing alongside for some of the time.

Hopefully Groups 2 and 6 will be found, and their successors benefit fully from the Group Work project in the future - Course ’23?

Course statistics, monitoring and evaluation

Lesson attendance

From 45 participants initially registered for the course, 15 attended at least 80% of live lessons, 10 attended 51-79% of lessons, 10 attended 1-50% of lessons. 10 participants were non-starters (registered, but did not complete at least one lesson or attend any tutorials). Lesson attendance per registered participant and distribution of participants relative to their lesson attendance are presented in **Figure 1.**

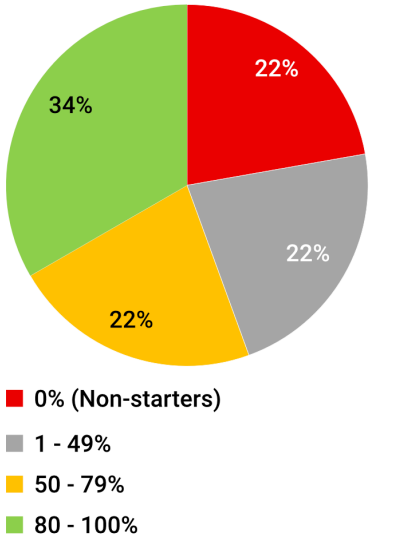

Figure 1: Attendance at the live tutorials per registered participant

Completion of course assignments

From 45 participants initially registered for the course, 2 participants completed at least 80% of Moodle assignments. 8 participants completed 51-79% of Moodle assignments. 23 participants completed 1-50% Moodle assignments. Completion of course assignments per registered participant and distribution of registered course participants relative to their task completion are presented in **Figure 2.**

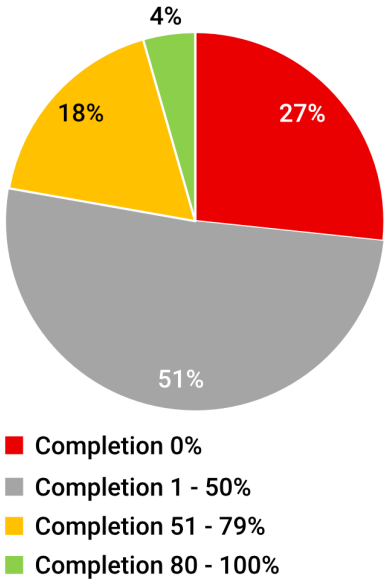

Figure 2: Completion of course assignments per registered participant

Group work presentations

Four out of six groups submitted their group assignment, presented their findings and received questions and feedback from the faculty and their peers. All 4 groups successfully passed the group work assignment.

End-of-course examinations

From 45 participants initially registered for the course, 24 participants achieved the end-of-course exam passing grade.

Monitoring and Evaluation

The baseline survey showed a response rate of 87,5%. Some participants defined rather general objectives without a time-specific component. Therefore further evaluation surveys were designed in a way that asked open questions where participants could flexibly describe examples of the knowledge implementation post-course. The end-of-course survey was conducted after all course activities were completed and had a response rate as of 10 February 2023 of 39%.

The key findings based on the end-of-course survey are presented in **Figures 3-5**.

An overview of output indicators included in the monitoring scheme, their achievement status as of 12 February 2023 are presented in **Table 1**.

As part of the evaluation phase, data regarding achievement of predefined objectives (outcomes) as well as barriers and enablers of knowledge implementation at the workplace of course participants will be collected at 3, 6 and 12 months post-course using further evaluation surveys.

The end-of course survey revealed strengths and weaknesses as detailed in the selected feedback below as well as fully detailed in Appendix 2 at the end of this document.

Program Strengths & Weaknesses

Selected comments from participants describing program strengths

“The course is comprehensive yet extensive enough to offer a complete understanding of the process from drug development phase to post-registration issues.”

“The course material on Moodle, weekly live interactions and discussions were exceptional. The biggest strength is online lessons (a better reach to other countries and for us all to learn from different perspectives) and the weekly group discussions on the current topics and the perspective from the specialists in the discussed topics.”

“Different experts sourced nationally and internationally to give lectures.”

Selected comments from participants describing program weaknesses

“There is limited time to learn or study, because we also had our jobs to fulfill the daily duties or deadlines.”

“Poor participation by some members in group assignments and high workload”

“The study material can be overwhelming, as it’s a lot of reading with limited time especially, when the workplace does not cater anytime for the participants to focus on the course. So, balancing between work and committing to the course and the group assignments can be overwhelming.”

Selected comments from participants describing learning format strengths

“I could learn at my own pace, it’s easy to plan ahead, I’d miss a lecture can always go through the recording at later stage or even at respected time as needed.”

“From a teacher-perspective group work offers different intellects, skill-sets, and critical

evaluation strengths to manage the presentation learning experience and to even teach other students, so this is viewed as a strength and beneficial to the learning experience."

"The groups for group work comprise of colleagues from the same regulatory agency Moodle is a great catch-all platform for learning and it is accessible from anywhere."

Selected comments from participants describing learning format weaknesses

"The self work could be overwhelming although the content is relevant and helpful."

"Too much pre-reading. In some weeks, the reading material and tasks were only loaded a few days before the lesson, even on the day of the lesson."

"The breakout rooms are intimidating especially when one has not received the question in advance and had time to prepare, as well as the fact that other participants just don't contribute leaving a few people to do the talking."

End-of-course survey

All responders to the end-of-course survey ranked the lessons offered as part of the course as moderately to extremely satisfactory with regards to their relevance for their daily work and how engaging the courses were (see **Figure 3**).

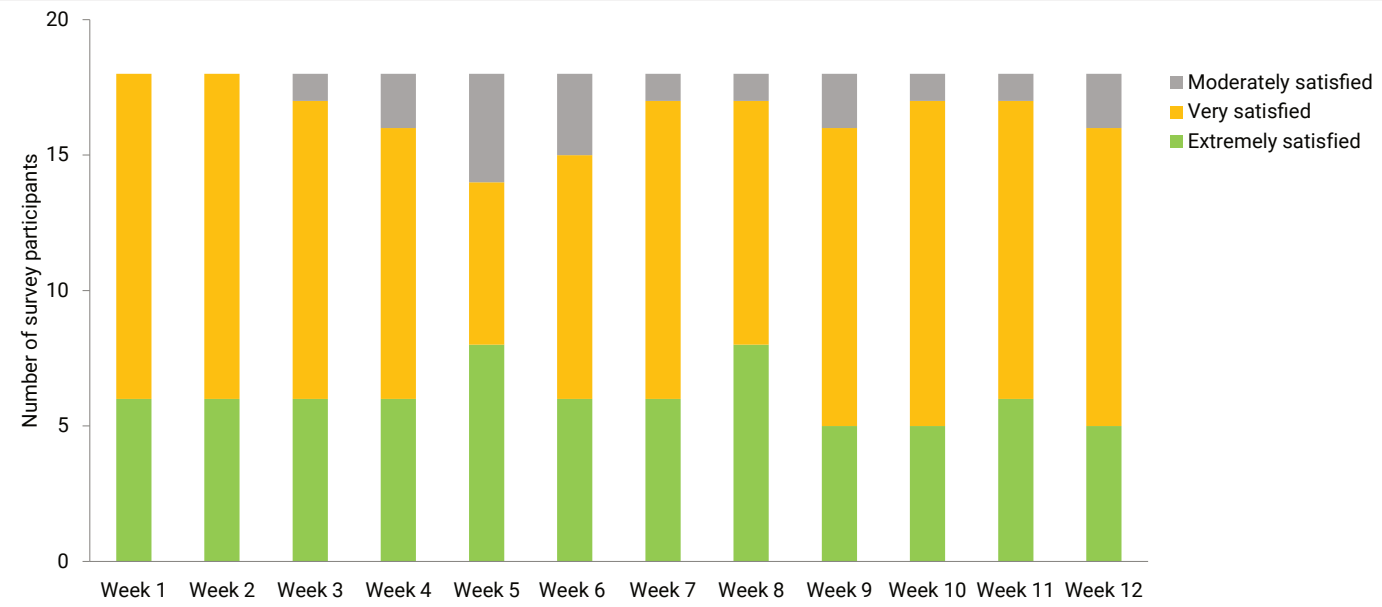

Figure 3: Course participants' satisfaction with course lessons with regards to relevance of the content to their daily work and how engaging the courses were.

From 18 responders to the end-of-course survey, 33% rated the course as extremely helpful in achieving their objectives in terms of regulatory performance, followed by 56% who rated the course as very helpful and 11% who rated the course as moderately helpful (see **Figure 4)**.

The end-of-course survey showed that 28% of responders are confident that they can immediately be successful in using what they learned as part of the course without more guidance or experience. 50% of respondents stated that they need more experience to be good at using what they learned, while 0% need more guidance in order to know how to use what they learned. 17% stated that their current role does not enable them to use what they learned. 5% are undecided on what to do and/or why to do it. Course participants' assessment of how able they are to put what they learned during the course into practice at their workplace is presented in **Figure 5**.

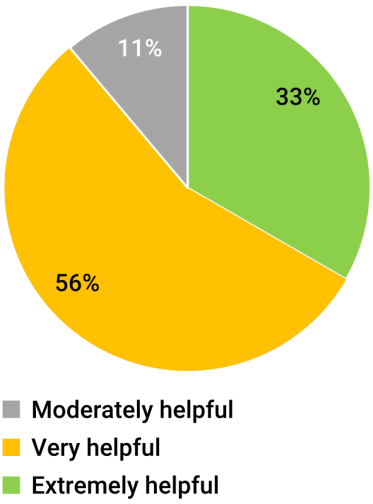

Figure 4: Course participants' perception of the helpfulness of the course regarding achieving their regulatory performance objectives

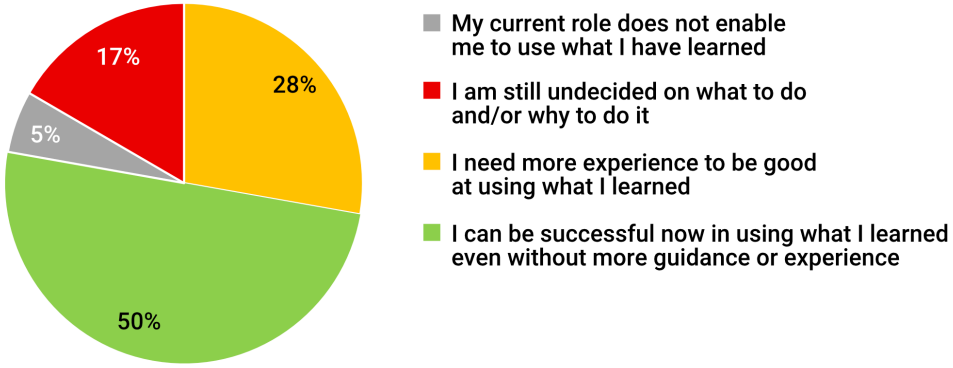

Figure 5: Course participants' assessment of how able they are to put what they had learned during the course into practice at their workplace.

Status of Output Indicators

All M&E activities to date were conducted and completed as planned. In total 5 indicators were included in the monitoring scheme (i.e. output indicators). An overview of output indicators, and achievement status are presented in **Table 3.**

Table 3: Overview of output indicators and achievement status as of February 2023.

Output Indicator as defined in M&E Framework	**Achievement Status / Recommendation**
During the course duration, live tutorial attendance by the registered participants is at least 80% . (45-10 non-starters=35; benchmark: 35x0.8=28)	Result: 15 participants participated in at least 80% of live lessons (0-12). 15/35=42%
By the end of the course, at least 80% of participants have successfully completed critical tasks on Moodle. (45-10 non-starters=35; benchmark: 35x0.8=28)	Critical tasks on Moodle have not been defined yet. Recommendation: identify tasks which are critical for knowledge transfer and focus on them in monitoring.
By the end of the course, at least 80% of participants have successfully passed the group work assignment. ((45-10 non-starters=35; benchmark: 35x0.8=28)	Result: 28 participants passed the group work assignment.
At least 80% of the participants who successfully completed the course and defined expectations/objectives prior course find this course moderately to extremely helpful in achieving their baseline objectives. (80%(# participants who earned the course certificate)=19)	End-of-course survey response rate: 39%.
At least 50% of participants who successfully completed the course feel that they can successfully use in their daily work what they learned even without more guidance or experience or with minimal help from experienced peers'. (50%(# participants who earned the course certificate)=12))	End-of-course survey response rate: 39%

Course Completion and Graduation Ceremony

Participants who successfully completed the course participated in a virtual graduation ceremony hosted by the University of Witwatersrand. A recording of the event is available at this link.

Conclusions and Next Steps

This program's aim to support the work of clinical assessors working in regulatory agencies in SAHPRA, Ghana FDA, PPB, NAFDAC, TMDA and MCAZ was successfully concluded as a University recognized short course. The valuable feedback collected from the completion of 2 cohorts will feed into running the next cohort.

The next steps will include:-

- Continue with the monitoring and evaluation plan that will collect further information on application of the learnings over the next 12 months post-participation in the course.
- Revise the content of the pilot course based on feedback from the pilot e.g.
  - Participants and their sponsoring agency will be fore-warned of their joint responsibility to ensure engagement of their staff in this training – focusing on participation and motivation to complete the certification. As an example, sponsors from the agencies must ensure time available to participate in the program
  - During the course, the program secretariat will ensure closer regular feedback and persuasion directly to the participants to help them conclude the assessment components.
  - Assessment components will be reviewed to ensure tighter alignment with program inclusion and to reduce redundancy where possible
- While the survey participation rate of 39% is consistent with the responses seen in other long-term surveys, nevertheless, this is disappointing given that the program is a sponsored activity that is free to the participants. The core-team will explore incentives such as linking the surveys with the certification: no survey completion, no certification!
- Run the adapted course with a new cohort
- Identify additional University partners across Africa
- Plan and establish new training modules on relevant prioritized topics

Acknowledgement of funding support

This project received financial support from the Bill & Melinda Gates Foundation.

Appendix 1: Faculty Bios

Arnold G. Vulto

Arnold G. Vulto (1952) obtained his pharmacy-degree from Groningen University (The Netherlands) in 1981, with undergraduate studies in Cambridge (UK). He was trained as a pharmacologist at the Rudolf Magnus Institute at the University of Utrecht and at the Karolinska Institute (Stockholm, Sweden).

In his career he developed an interest in biological medicines and has been involved in biosimilars since 2004. He is a Qualified Person for biotechnology medicines.

Professor Vulto is one of the co-founders of the Generics & Biosimilars Initiative (GaBI; 2008) and the Initiative Group Biosimilars The Netherlands (2013). In 2016 he was one of the founders of the MABEL Research Fund at Leuven University, Belgium.

Liese Barbier

Liese Barbier, PharmD, PhD, is a Postdoctoral researcher at the KU Leuven in Belgium, where she is part of the Regulatory Sciences & Pharmaco-Economics research unit.

Her research interests and activities focus on optimizing regulatory, clinical and HTA/payer decision-making frameworks. She has a particular interest in complex therapies such as biologicals including biosimilar medicines, medicine development in areas of high unmet medical need, and the integration of patient preference research data in decision-making. Liese's PhD research focused on regulatory, clinical and policy challenges related to biosimilar regulatory evaluation and market entry in Europe, through which multi-stakeholder informed recommendations were generated to foster sustainable off-patent biological market dynamics. In 2019, Liese was seconded to the European Medicines Agency as National Expert. Here, Liese was part of the Oncology, Haematology and Diagnostics office of the Human Medicines Evaluation Division and focused as Product Lead on the evaluation of biosimilar candidates in oncology. Further, Liese provided scientific input and support to biosimilar related initiatives across the Agency and coordinated as Scientific Lead the Biosimilar Medicinal Products Working Party.

Liese Barbier obtained her PharmD at KU Leuven in 2015, after which she gained clinical experience as a pharmacist in the in- and outpatient setting.

Birka Lehmann

Dr Birka Lehmann is Senior Expert for Drug Regulatory Affairs and Lecturer at the University of Bonn since 1998.

Birka Lehmann studied Medicine at the Free University Berlin. Her working experience includes 9 years preclinical assessment in the division 'Pharmacology and Toxicology' of BfArM (Federal Institute for Drugs and Medical Devices) and she served as head of unit 'Decentralised Procedure' (1996-2002) and as deputy head of EU Division (2000-2002). She was member of and chaired the Mutual Recognition Facilitation Group and served as expert to the Committee for Human Medicinal Products (EMA).

From 2002 – 2006 she joined the European Commission, Directorate-General Enterprise and Industry as expert on secondment to in the unit 'Pharmaceuticals' responsible for inter alia Marketing Authorisation and implementation of Clinical Trials Directive.

From 2006 - 2011 she was head of the division 3 Marketing Authorisation procedure and from 2011 – 2016 head of Executive Department EU and International Affairs (BfArM).
She was a member of the Paediatric Committee at the European Medicines Agency from 2007 - 2016.

Sunaina Indermun

Dr Sunaina Indermun completed her Bachelor of Pharmacy degree in 2011 at the University of the Witwatersrand and joined the Wits Advanced Drug Delivery Platform (WADDP) in 2012, under Prof. Viness Pillay, where she completed her PhD in 2014. The primary focus of her pharmaceutics-based PhD research project was the development and testing of a novel drug delivery system which allowed for the transdermal, electro-responsive release of a therapeutically effective agent through a microneedle patch-like device.

In 2016, Dr Indermun re-joined WADDP as a post-doctoral research fellow after completing her community service and has shown a keen interest in the field of pharmaceutics, integrating various interdisciplinary scientific concepts. Her specialities also include 3D-printed drug delivery system design and formulation, tissue engineering for biological tissue regeneration and replacement, as well as commercial product development for multiple local and

international pharmaceutical and veterinary companies. Dr Indermun has resultantly through her research generated more than 20 ISI-accredited papers and has presented at numerous international conferences, more recently, as one of the selected South African representatives at the 5 th BRICS Young Scientist Forum held virtually in Russia and the Lindau Nobel Laureate Meeting held virtually in Lindau, Germany.

She currently is an associate medical writer at Nucleus Global and is a guest lecturer at the Department of Pharmacy and Pharmacology, University of the Witwatersrand, specialising in clinical trial courses.

Memela Makiwane

Dr Memela Makiwane is a consultant clinical pharmacologist at Dr George Mukhari Academic Hospital (DGMAH) and senior lecturer at Sefako Makgatho Health Sciences University (SMU). Memela is a member of 2 expert review committees of the National Essential Medicines List Committee (NEMLC); serves on the Pharmacovigilance Committee (PVC) of the South African Health Products Regulatory Authority (SAHPRA); and serves on the antimicrobial resistance (AMS) Ministerial Advisory Committee (MAC) of South Africa. He is the current Chairperson of the Council for Medical Schemes (CMS).

Luther Gwaza

Luther Gwaza has fifteen years experience in pharmaceuticals, of which more than ten years is in

the regulation of medical products and in designing curriculum/teaching/learning materials and lecturing at university level and vocational training. He spent the last four years in Geneva working for the World Health Organization (WHO) headquarters, supporting access to medicines and health technologies in low- and middle-income countries by facilitating national registrations of medical products recommended by WHO- prequalification and from other reference authorities.

Luther started his career as a pharmaceutics lecturer at the University of Zimbabwe in 2007 until 2012. He also worked as a consultant regulatory officer for the national medicines regulatory authority (NRA) in Zimbabwe from 2007 until 2017. He has consulted for WHO, Management Sciences for Health, and World Bank Group, among others, on medicines regulation in Africa and Asia.

Luther was a visiting Fogarty Research Fellow at the School of Pharmacy, University of California San Francisco (UCSF), United States, 2006, and 2010, working on pharmacokinetics and drug interactions. He has published scientific articles in peer-reviewed journals on drug interactions and bioequivalence. He holds a Bachelor of Pharmacy (honours) and a Master of Philosophy (MPhil) in pharmacology, both from the University of Zimbabwe and a Ph.D. in Pharmaceutical Policy and Regulation from The Utrecht University.

Colin Pillai

Goonaseelan (Colin) Pillai is committed to driving programs that develop scientific capability in low and middle-income countries.

A clinical pharmacologist who trained in Durban, South Africa, Colin previously worked at the corporate headquarters of Novartis and Roche in Switzerland. He has a specialist interest in the application of non-linear mixed effects models to pharmacokinetic-pharmacodynamic data across a wide range of therapeutic areas.

In Pharma, he played leadership roles in bringing internal and external acceptance of applying mathematical models to decision making in drug development. His most recent Pharma role involved establishing programs that allowed sharing scientific expertise and infrastructure with researchers and institutions in LMIC.

Colin has held teaching, research and management positions at the Universities of Durban-Westville and Witwatersrand. He acquired his clinical and research experience in hospital and community pharmacy and as a consultant with the SA Medical Research Council's Tuberculosis Research program, where he ran a unit conducting Phase 1 clinical trials. Colin continues to maintain active academic links with numerous institutions in Africa including via formal Honorary Professorships and Board Member status. Since November 2017, he is a Senior Advisor on capacity development and training programs for global health to the Bill and Melinda Gates Foundation.

Peter Stonier

Peter Stonier is a Fellow of the Academy of Medical Sciences, UK. He is visiting Professor, King's College London, Centre for Pharmaceutical Medicine Research. He is Director of Specialty

Training, Faculty of Pharmaceutical Medicine, Royal Colleges of Physicians UK, where he is national programme director for pharmaceutical medicine specialty training.

A career pharmaceutical physician, Peter has experience in medicines development, medical affairs, clinical research and pharmacovigilance. He served as medical director & board member of the Hoechst Marion Roussel UK group (now Sanofi), and later was group medical director Amdipharm plc.

Peter is a founding Fellow of the Faculty of Pharmaceutical Medicine, which he formerly served as president. An executive board member of the PharmaTrain Federation, Brussels, and a founding Fellow of the Belgian College of Pharmaceutical Medicine, Peter is past President of the International Federation of Associations for Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP). He was awarded a lifetime achievement award by the Academy of Clinical Research Professionals, Washington DC for his contribution and leadership in the field of pharmaceutical medicine.

Peter graduated in physiology with a doctorate in protein chemistry, Universities of Birmingham & Sheffield, and qualified in medicine from the Manchester Medical School.

His publications include texts in pharmaceutical medicine & edited works in clinical research, paediatric clinical research, medical affairs and in human psychopharmacology.

Bernd Rosenkranz

Prof Emeritus Bernd Rosenkranz has a medical degree and is board certified Pharmacologist and Clinical Pharmacologist in Germany and South Africa, affiliate of the College of Clinical Pharmacologists (CMSA) and Fellow of the UK Faculty of Pharmaceutical Medicine (FFPM).
He spent 23 years in industry, as Director of Clinical Pharmacology at Hoechst/Hoechst Marion Roussel in Germany, France and USA, Chief Medical Officer at 3ClinicalResearch in Berlin, Germany, and Vice President Clinical Development at Jerini, Berlin, Germany. From 2008 until 2016, he was Professor/Chief Specialist in Pharmacology and head of the Division of Clinical Pharmacology, Stellenbosch University, where he established a postgraduate programme in Pharmaceutical Medicine / Medicines Development (PharmaTrain Centre of Excellence). He is visiting scientist at the Institute for Clinical Pharmacology and Toxicology, Charité, Berlin, and supervises two PhD students with pharmacovigilance research projects performed in South Africa and Ghana. Bernd Rosenkranz is President of the Fundisa African Academy of Medicines Development which offers courses and workshops on medicines development and regulation. He is Honorary Member of the South African Society for Basic and Clinical Pharmacology (SASBCP), and member of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP), the European PharmaTrain Federation, and the Association for Applied Human Pharmacology (AGAH) in Germany. He was Chair of the South African Congress of Pharmacology and Toxicology (SACPT 2010), Finance Chair of the 17th World Conference of Basic and Clinical Pharmacology (WCP2014), and is Finance Chair of the 3rd World Conference on Pharmacometrics (held in Cape Town in 2022). He is convener of a sub-team involved in preparing the South African COVID-19 Country Report. Bernd Rosenkranz is peer reviewer for several journals, and has acted as reviewer for the South African National Research Foundation

and as external examiner for several Universities in South Africa. His work is presented in more than 110 original publications, 17 book chapters, and more than 170 oral or poster presentations. He is Associate Editor of Frontiers in Pharmaceutical Medicine and Outcomes Research. Bernd Rosenkranz is vice treasurer of the Manenberg Aftercare Centre, Cape Town and airport chaplain in Berlin, Germany.

Gabriel McClelland

In the midst of a seemingly infinite landscape of soulless, dull, and otherwise unqualified communicators, there is still hope. Here is a person who knows the fine line between rock-solid management and improvised genius. He knows the difference between good and evil, and isn't afraid to use both to get the job done. For him, breakfast comes with a dose of unfettered creative energy and dinner is served with the satisfaction of a job well done. Does this sound too good to be true? Think again. You're reading his bio.

Phumla Sinxadi

A/Prof Phumla Sinxadi is a consultant clinical pharmacologist, as well as an Associate Professor of Medicine in the Division of Clinical Pharmacology, University of Cape Town (UCT), South Africa Phumla teaches clinical pharmacology to undergraduate and postgraduate students at UCT.

Her main research interests include i) pharmacokinetics and pharmacogenomics of antiretroviral drugs; ii) gene-gene interactions between antiretroviral and antituberculous drugs, iii) drug development. She was the lead investigator for the First-in-Man clinical trial investigating the safety, tolerability and pharmacokinetics of MMV390048, a novel antimalarial drug discovered at UCT. 1st African First Into Human study for an antimalarial compound for an African led international collaborative project.

She received her PhD degree in Clinical Pharmacology from the University of Cape Town in 2016, a Masters of Medicine in Clinical Pharmacology in 2010, and a Bachelor of Medicine and Surgery degree in 2001. In 2017, she completed a Certificate in Human Pharmacology from the Faculty of Pharmaceutical Medicine of the Royal College of Physicians in the United Kingdom.

After completing her PhD, she spent a year at GlaxoSmithKline (London) as a WHO-TDR Career Development Fellow

John Woodland

John is a chemist with interdisciplinary research experience and a passionate interest in developing molecular strategies, such as treatments and tools, to tackle the scourge of infectious disease. He is currently a Junior Research Fellow at the Drug Discovery and Development Centre (H3D) at the University of Cape Town (UCT), conducting research in chemical biology and medicinal chemistry aspects of malaria and tuberculosis drug discovery. John is also passionate about using his skills to promote science and to improve scientific literacy in South Africa.

Ivana Škrnjug

Ivana Škrnjug is committed to strategic planning and monitoring and evaluation of regulatory capacity strengthening interventions in low and middle-income countries.

Ivana is a molecular biologist who specialized in chemistry, manufacturing and control (CMC) of biologics through positions in academic research, industry and a regulatory authority. Currently she works in the pharmaceutical industry as a global regulatory affairs CMC manager. Being passionate about global health, Ivana is currently enrolled in an MBA programme in International Health Management (Swiss TPH). As part of the MBA programme Ivana is focusing on understanding the mechanisms crucial for access to medicines and strategies for evaluation of effectiveness of capacity strengthening interventions.

Previously she worked at the Paul-Ehrlich-Institut, German Federal Institute for Vaccines and Biomedicines, as a CMC assessor and regulatory capacity strengthening expert. As part of the RegTrain-VacTrain project, a project of the German Federal Ministry of Health focusing on development of the scientific and regulatory capacity in African partner countries, Ivana conducted activities in close collaboration with the World Health Organization (WHO) and various African and international organizations. Ivana led the development of tools for validation of results collected during WHO self-benchmarking exercises and design of capacity strengthening plans tailored to the local needs and priorities of partner countries. Furthermore, Ivana contributed to development of RegTrain-VacTrain logical framework and monitoring and evaluation strategy.

Over the years she served as a speaker and facilitator in various workshops related to medicinal product development and CMC. In her latest publication she discussed the European system of reliance as a blueprint for increasing access to safe and efficacious medicines (Škrnjug et al., 2019).

Kennedy Otwombe

Kennedy is an expert biostatistician with 13 years of experience in his field. He is currently the Associate Professor, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa.

Stuart Walker

Professor Stuart R Walker BSc PhD MFPM FRSC FIBiol FRCPath, is an Independent Consultant in Pharmaceutical Medicine, Founder of both CMR International & the Centre for Innovation in Regulatory Science (CIRS), Professor of Regulatory Science, University of Hertfordshire, as well a Fellow of the School of Pharmacy, London University

Professor Walker spent ten years at London University which included lectureships in biochemical pharmacology at St Mary's Hospital Medical School and Clinical Pharmacology at the Cardiothoracic Institute. This was followed by eight years with Glaxo Group Research in the UK where he had international responsibility for several major clinical research programmes.

His current research interests include studies to improve productivity, efficiency and decision-

making in global drug development and the regulatory review process, developments in the Regulatory Environment in the Emerging Markets of the Asia-Pacific Region, Latin America, Africa & the Middle East, as well as public policy issues that relate to these research activities.

During his research career, Professor Walker has supervised over twenty-five PhD programmes, co-authored 350 research papers, co-edited twenty-four books in the fields of toxicology, drug discovery, clinical development, Regulatory policies, the Benefit/Risk Assessment of Medicines and Quality Decision Making Practices

Professor Walker has been a member of a number of academic, professional and industrial committees and participated in the editorial boards of several scientific journals. He was given the “Drug Information Association” Outstanding Service Award in 2001 and received a Lifetime Achievement Award from Informa in the same year & the TOPRA lifetime achievement award in 2011.

He is frequently involved in the organisation of national and international meetings on key issues that concern the pharmaceutical industry and the Regulatory Review of Medicines and has lectured extensively throughout Europe, the United States, Japan and the Asia-Pacific Region, Latin America as well as Africa and the Middle East. (September 2021)

Villyen Motaze

Nkengafac Villyen Motaze works passionately towards improving healthcare research in Africa.

Villyen is a Cameroonian medical epidemiologist currently based at the National Institute for Communicable Diseases (NICD). Villyen completed his medical studies Yaoundé, Cameroon before moving to Cape Town, South Africa, where he completed his masters and PhD in Epidemiology.

Villyen Joined the NICD in 2014 where currently works. He carried out several surveillance and research projects on vaccine-preventable diseases including measles, poliomyelitis, rubella and viral hepatitis. Villyen’s areas of interest include infectious diseases, vaccine preventable diseases, child health and reproductive health. He has a passion for training of post-graduate students and has supervised several masters students. He conducts systematic reviews of healthcare interventions and facilitates training on systematic reviews and Evidence-Based Practice.

Villyen is currently the head of the Notifiable Medica Conditions Surveillance System for South Africa and a consultant epidemiologist with the World Health Organization (WHO). His work with WHO includes epidemiological support for the COVID-19 response. He has previously worked on outbreak preparedness and response activities during the 2018 ebola outbreaks in the Democratic Republic of Congo. Villyen is a member of the newly established Cochrane Cameroon and a member of the Cochrane Africa Network.

Ingrid Klingmann

Physician, specialized in General Medicine, Clinical Pharmacology and Pharmaceutical Medicine with over 30 years of experience in different senior medical, operational and managerial

functions in pharmaceutical industry, CROs and clinical trial sites with focus on clinical trial design and management, ethical and regulatory aspects. Since January 2003 she has her own pharmaceutical development and site management support consulting company.

Dr Klingmann is Chairman of the Board of the European Forum for Good Clinical Practice (EFGCP). On behalf of EFGCP she was and is involved in different FP7- and IMI-funded projects (ICREL, PatientPartner, PharmaTrain, EUPATI, Combacte-NET, PARADIGM, ConCEPTION, PharmaLedger) and with her company in the FP7-funded paediatric LENA project. Her broad professional background as physician with experience in patient care, clinical development, site management, regulatory affairs, clinical research ethics, and patient engagement enables Dr Klingmann to bridge the gaps between the interests and skills of all different stakeholders in medicines development with the aim to develop new patient-relevant treatments more efficiently.

Dr Klingmann is also President of PharmaTrain Federation, the not-for-profit organisation focusing on global standardisation and improvement of post-graduate training in medicines development sciences. She also teaches on different clinical research and regulatory affairs topics in diploma and master courses at the University of Bonn, Germany, University of Basel, Switzerland, and the Université Libre de Bruxelles, Belgium.

Leander Fontaine

Educated as a physician, Leander Fontaine worked from 1980 to 1988 in Germany in internal medicine and then specialized in anesthesiology. He is principal consultant at Pharmiceutics LLC, a consulting firm based in Pennsylvania, USA. Pharmiceutics is specialized in consulting, education and practical services in the areas of global/core labeling content and practices (including Company Core Safety Information), US labeling and EU labeling.Pharmiceutics' client base is in the US, in Europe and in Asia and includes many large, mid-size and small pharmaceutical companies.

Eric Karikari-Boateng

Eric is a Senior Reviewer of non-clinical and clinical data supporting Marketing Authorization Applications and Clinical Trial Authorization at the Food and Drugs Authority, Ghana. He is a Pharmacist by training and holds a Master's degree in Pharmacy (Pharmacology and Toxicology) and has over fifteen (15) years' experience in the review of nonclinical and clinical data (CTD modules 4 and 5) covering small molecules, well characterized biologics/biosimilars and vaccines

Elimika Pfuma Fletcher

PharmD, PhD, is a Senior Clinical Pharmacologist serving as a Policy Lead in the Office of Clinical Pharmacology (OCP) at the US FDA. Her current primary areas of focus are pediatrics and maternal health. She has over 11 years of regulatory experience at the FDA with expertise in many aspects of clinical pharmacology including genomics, biologics and biopharmaceutics. She previously served as a Senior Clinical Pharmacology Reviewer supporting Oncology drug products from 2009-2016. She received a Doctor of Pharmacy (PharmD) degree in 2008 and a PhD in

Pharmaceutical Sciences in 2009 from the University of Houston College of Pharmacy.

Sam Salek

Sam Salek is Professor of Pharmacoepidemiology in the School of Life and Medical Sciences, University of Hertfordshire, UK where he leads the Public Health & Patient Safety research group. He is also the Director of the Institute for Medicine Development, Cardiff, UK, VicePresident of PharmaTrain Federation and a visiting Professor at the State of Hessen, Germany. Professor Salek is the founder and past chair of the Patient Engagement Special Interest Group of the International Society of Quality of Research, co-chairs the European Hematology Association (EHA) Scientific Working Group for Quality of Life and Symptoms and chairs the EHA SWG 'Gaucher's Disease Task Force'.

Shabir Banoo

Shabir Banoo holds the position of Chief Technical Specialist and Head: Pharmaceutical Policy and Programmes within Right to Care, a donor-funded non-profit organisation linked to the University of the Witwatersrand. In this role, he oversees Right to Care's pharmaceutical technical assistance, research and support programmes to ministries of health in South Africa and several other African countries. The focus of this work is aimed at strengthening pharmaceutical policy, regulation and governance in public health programmes through implementation of best practices to improve patient management and care, particularly for HIV and related diseases.

Regine Lehnert

Regine Lehnert is a senior clinical assessor at the Federal Institute for Drugs and Medical Devices (BfArM), one of Germany's medicines regulatory authorities. She is trained as a medical doctor with special expertise in infectious diseases.

With experience in conducting clinical trials (HIV and related diseases) and drug licensing in different therapeutic areas (e.g. rheumatology and oncology/immunology), she has been working in the area of infectious diseases for the past 16 years.

She is a member of the Infectious Disease Working Party at the European Medicines Agency and the German Expert Advisory Board on Pandemic Acute Respiratory Infections. For more than 15 years she has been advisor to the WHO Prequalification Programme for medicines.

Since 2019 she has been leading the "GHPP-Pharmtrain Project", partnering with a number of African national medicines regulatory authorities in structure- and capacity-building.

Appendix 2: Verbatim Comments from Participants

Verbatim comments from participants describing program strengths

- The facilitators are the biggest assets for this course, their shared experience in their respective fields provide an overview of real-world practice and knowledge.
- Different experts sourced nationally and internationally to give lectures.
- The course helps in acquiring knowledge that makes one a better regulator officer.
- The faculty members are very well versed with the content and are also very dedicated and patient with the learners and that's a major strength.
- Very informative and relevant to regulators
- The course is comprehensive yet extensive enough to offer a complete understanding of the process from drug development phase to post-registration issues.
- The lectures and resources lead an engaged student to research more and learn more as needed.
- The lecture notes and references provided weekly on Moodle-platform are helpful.
- The course material on Moodle, weekly live interactions and discussions were exceptional. The biggest strength is online lessons (a better reach to other countries and for us all to learn from different perspectives) and the weekly group discussions on the current topics and the perspective from the specialists in the discussed topics.
- A lot of knowledge to learn
- Diversity of regulatory experience amongst the student group. The vast array of faculty lecturers
- The good quality and completeness of the study material
- The presenters were knowledgeable
- Content assignment
- Competent faculty, and use of group work/ breakouts.
- The biggest strength, I believe, are the knowledgeable facilitators and the course material provided

Verbatim comments from participants describing program weaknesses

- Short time
- I wish materials for the following week's work could be posted on a Friday so that the participant may use the weekend to prepare.
- Unfortunately, during the week, we had to prioritize deliverable as per our respective Job Description
- The study material can be overwhelming, as it's a lot of reading with limited time especially, when the workplace does not cater anytime for the participants to focus on the course. So, balancing between work and committing to the course and the group assignments can be overwhelming.
- I was a bit intimidated in the breakout sessions, however I understood the objective of this activity. If I could take the course again, I would - especially when I start handling dossiers with clinical data.
- The one weakness that stands out for me is that I didn't have as much time as I would have loved to dedicate to the course. This is because my work obligations did not allow, this made it challenging to go through the material provided on Moodle.
- Little too packed and difficulty concentrating during the live session since it is organized during working hours.
- There is limited time to learn or study, because we also had our jobs to fulfill the daily duties or deadlines.
- Weekly lessons require more time for completion, it is too saturated with not enough time.
- Too many weekly assessments to be completed in little time.
- self-study assignments were quite a lot to handle considering you are busy doing day to day work.
- time restrictions to the slides the presenters are granted... and sometimes they just gloss through the content.
- Poor participation by some participants.
- Poor participation by some members in group assignments and high workload

Verbatim comments from participants describing the strengths of the learning format

- Every aspect of the course was equally effective
- The moodle was pretty easy to navigate
- The Moodle always enabled access to live sessions missed
- I could learn at my own pace, it's easy to plan ahead, I'd miss a lecture can always go through the recording at later stage or even at respected time as needed.
- Live lessons, moodle and group work are strength
- As a postgraduate course, the chosen format of Moodle-platform-based, live lessons + self-learning + presentations (which offer case study type learning) are effective and considered to be strengths. From a teacher-perspective group work offers different intellects, skill-sets, and critical evaluation strengths to manage the presentation learning experience and to even teach other students, so this is viewed as a strength and beneficial to the learning experience.
- Moodle Platform is very convenient and easy to maneuver
- The good quality and completeness of the study material
  The "inter-activeness" of the live sessions
- The groups for group work comprise of colleagues from the same regulatory agency
  Moodle is a great catch-all platform for learning and it is accessible from anywhere.
- The live session was seamless
- Quite involving
- The live sessions and group-work was interactive
- I believe that the strengths were the live lessons.

Verbatim comments from participants describing the weaknesses of the learning format

- The breakout rooms are intimidating especially when one has not received the question in advance and had time to prepare, as well as the fact that other participants just don't contribute leaving a few people to do the talking.
- The Moodle-Platforms are not Interactive, they can be replaced with more quizzes as they take too much time
- Network instabilities sometimes, otherwise it's a very recommendable way of teaching
- From a student-perspective this was the greatest weakness of this current course and a difficulty to my learning, time management and patience with disinterested people: 4 out of 7 group members became interested and engaged in the presentation just 3 days prior to the due date (and only after 20 slides were shared by me). I had to spoon-feed what to do and where to find information at this late-stage. The allocated weekly groupwork tasks were not completed by many. 2 people ignored most of the group's meetings till the week that the presentation was due. Metaphorically speaking I had to build the house till roof level (presentation slides) with mainly 1 other intelligent lady, before the others came to do a bit of decoration.
- The self work could be overwhelming although the content is relevant and helpful.
- The timing should also not coincide with the Christmas holiday period as most people are traveling and maybe difficult to get hold of group members.
- Too much pre-reading. In some weeks, the reading material and tasks were only loaded a few days before the lesson, even on the day of the lesson!
- The Moodle-platform was a little difficult to navigate, especially with the group work sections, it wasn't clear if we were to submit group weekly assignments.