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# Experience and problems encountered during the whole FDA BLA submission and review cycle of an oncology drug

Presented by
Lihong Wen, Senior Manager, Statistical Programming, Clin-nov
26th Aug 2023

# Meet the Speaker

## Lihong Wen

Title: Senior Manager of Statistical Programming

Organization: Tianjin Clin-nov Medical Technology Co., Ltd.

Lihong is the statistical programming senior manager at Tianjin Clin-nov Medical Technology Co., Ltd., she has nearly 10 years experience in statistical programming and biostatistics for both CRO and pharmaceutical company.

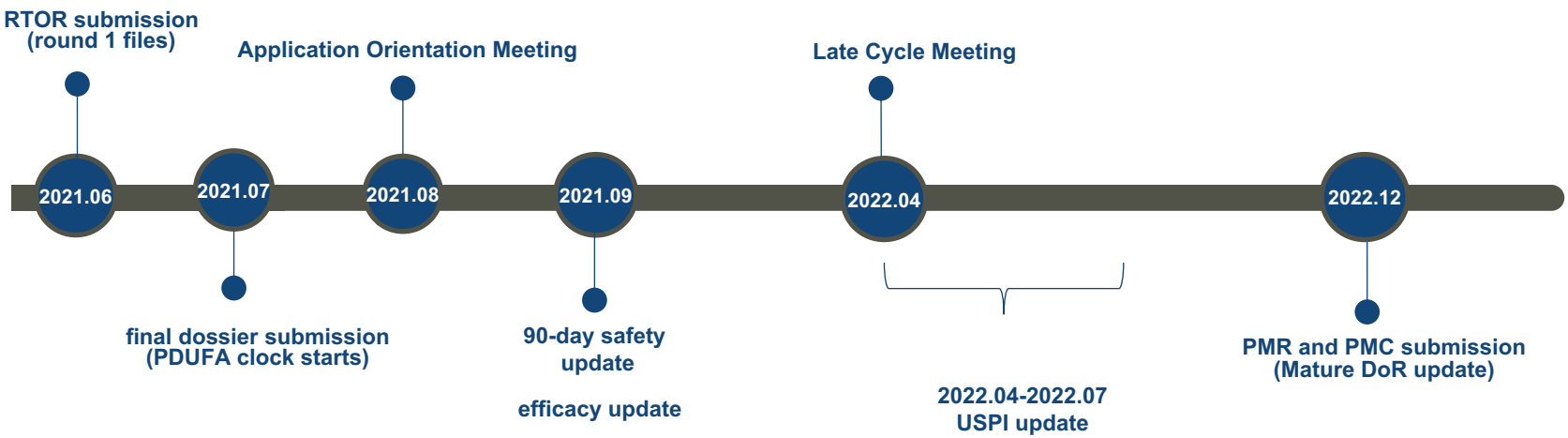
# Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

# Agenda

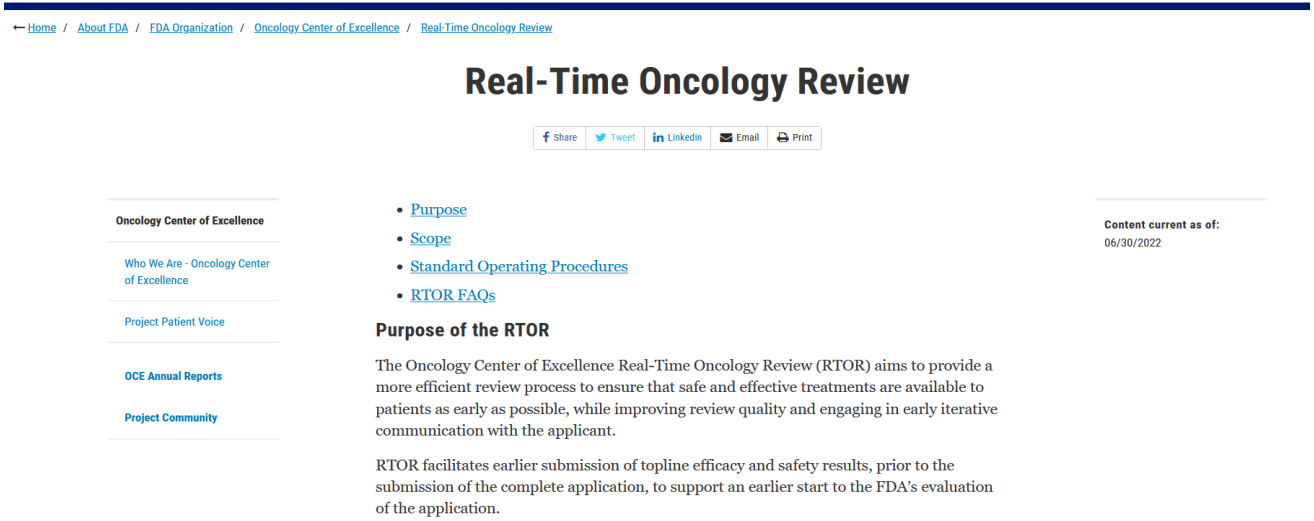
1. Submission and review cycle
2. Real-Time Oncology Review and Assessment Aid
3. Bioresearch Monitoring (BIMO)
4. AOM - Datasets walkthrough meeting
5. 90-day safety update report
6. efficacy update and mature DoR update
7. United States Prescribing Information

# Submission and review cycle



# Real-Time Oncology Review and Assessment Aid

- RTOR pilot



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## Real-Time Oncology Review

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**Oncology Center of Excellence**

Who We Are - Oncology Center of Excellence

Project Patient Voice

**OCE Annual Reports**

**Project Community**

- Purpose
- Scope
- Standard Operating Procedures
- RTOR FAQs

**Purpose of the RTOR**

The Oncology Center of Excellence Real-Time Oncology Review (RTOR) aims to provide a more efficient review process to ensure that safe and effective treatments are available to patients as early as possible, while improving review quality and engaging in early iterative communication with the applicant.

RTOR facilitates earlier submission of topline efficacy and safety results, prior to the submission of the complete application, to support an earlier start to the FDA's evaluation of the application.

**Content current as of:**
06/30/2022

**To learn more about real-time oncology review, go to:**

**FDA website: https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review**

**White Paper: Friends of Cancer Research. (2018). Real-Time Oncology Review and the Assessment Aid: Increase Review Efficiency Through Standardization and Earlier Data Access**

# Real-Time Oncology Review and Assessment Aid

- **RTOR Successful case study**

**The first approval made through the RTOR pilot was ribociclib (trade name: Kisqali).**

Figure 1: Timeline for RTOR submissions*

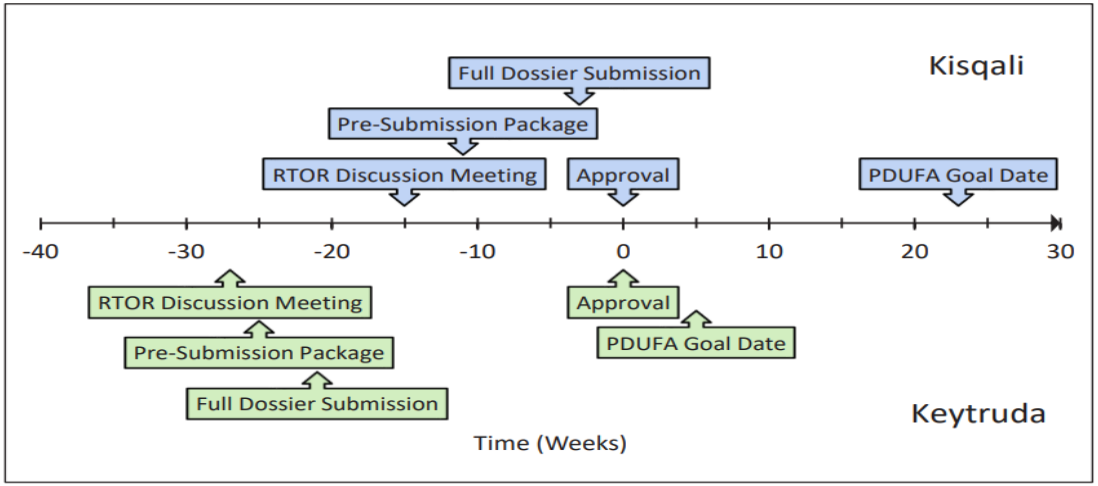



Table 3: Novartis RTOR Timeline

| Event Date | Action | Not |
|---|---|---|
| January 2018 | Pre-NDA meeting held with FDA | |
| April 6, 2018 | Novartis/FDA RTOR discus-sion | |
| April 24, 2018 | Pre-submission packages start to be sent to FDA | • |
| April-June 2018 | FDA issues multiple IRs | |
| June 28, 2018 | Full dossier submission | • |
| July 18, 2018 | sNDA for Kisqali approved | |

# Real-Time Oncology Review and Assessment Aid

- **Assessment Aid**


**To learn more about Assessment Aid, go to:**

**FDA website: https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid**

**White Paper: Friends of Cancer Research. (2018). Real-Time Oncology Review and the Assessment Aid: Increase Review Efficiency Through Standardization and Earlier Data Access**

# Real-Time Oncology Review and Assessment Aid

- **Assessment Aid Template**

8.2.4. **Safety Results**

**Deaths**

Data:
[To the Applicant: Insert text here]

- **Sample Table: Summary of Deaths** [Replace this title with a Table Caption using the *Insert Caption* button in the Cross-Reference tab.]

| | Treatment Group N=X n (%) | Control Group N=X n (%) |
|---|---|---|
| **Total Deaths** | | |
| Due to progressive disease | | |
| Due to adverse event | | |
| Due to other reasons | | |
| Other: | | |
| **Within 30 days after last dose** | | |
| Due to progressive disease | | |
| Due to adverse event | | |
| Due to other reasons | | |
| Other: | | |
| **Beyond 30 days after last dose** | | |
| Due to progressive disease | | |
| Due to adverse event | | |
| Due to other reasons | | |
| Other: | | |

Source:

- **Sample Table: Grade 5 Adverse Events** [Replace this title with a Table Caption using the *Insert Caption* button in the Cross-Reference tab.]

| Adverse Event | Treatment Group N=X n (%) | Control Group N=X n (%) |
|---|---|---|
| **Deaths due to Adverse Event** | | |
| Preferred term (PT) | | |

Source:

- **Sample Table: Grade 5 Adverse Events within 30 days of Last Dose of Study Drug** [Replace this title with a Table Caption using the *Insert Caption* button in the Cross-Reference tab.]

| Study Arm | Subject ID | Age/Gender | Study Day of Death | Cause of Death | Related to Study Drug (Y/N) |
|---|---|---|---|---|---|
| | | | | | |

Source:

The Applicant's Position:
[To the Applicant: Insert text here]

The FDA's Assessment:
[FDA will complete this section.]

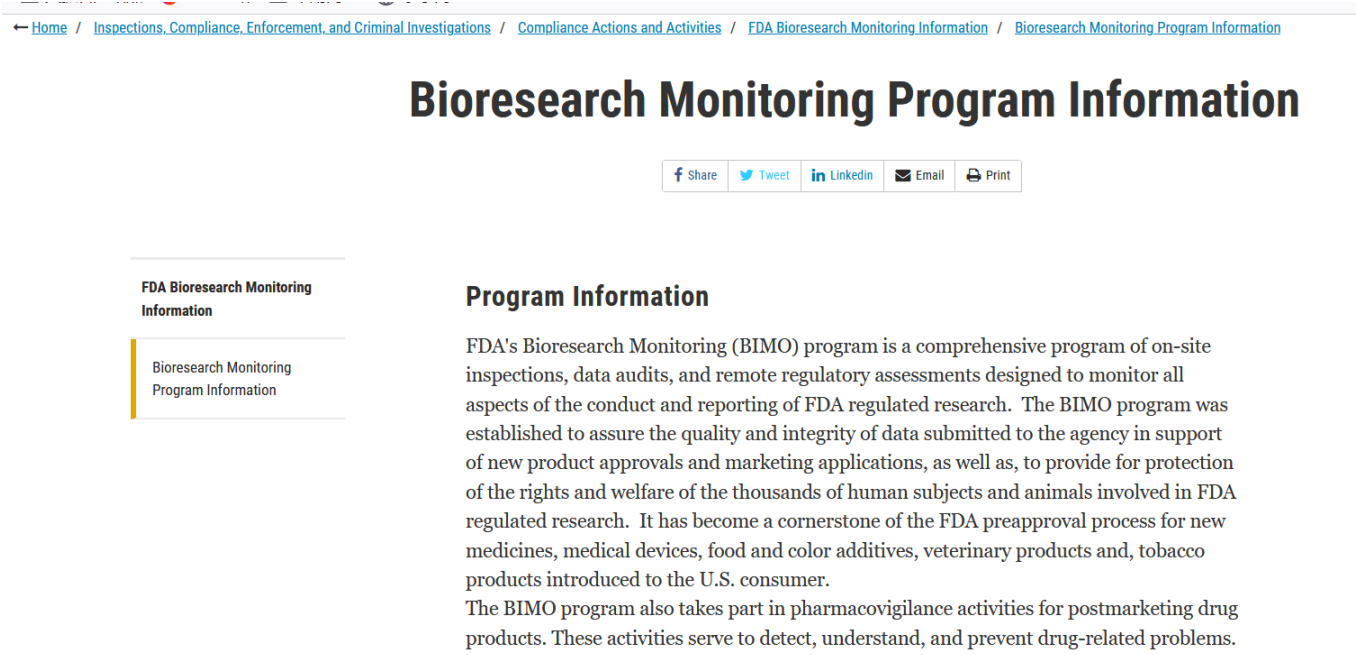
**FDA prefers the Assessment Aid (AAid) be used with RTOR.**

# Real-Time Oncology Review and Assessment Aid

- **RTOR pre-submission files**
  - ✓ Complete STDM and ADaM dataset package and supporting documents for pivotal study
  - ✓ Topline safety/efficacy TLF for pivotal study
  - ✓ SAS programs for pivotal study
  - ✓ Protocol, amendments and SAPs for pivotal study
  - ✓ Summary of data supporting dose selected for pivotal study
  - ✓ **ISS datasets**
  - ✓ Key analyses and datasets for clinical pharmacology (including popPK and ER)
  - ✓ User fee
  - ✓ Final reports module 4
  - ✓ Patient narratives
  - ✓ Proposed labeling
  - ✓ CRFs
  - ✓ All CMC information
  - ✓ **Assessment Aid**

# Bioresearch Monitoring (BIMO)

- BIMO overview



Home / Inspections, Compliance, Enforcement, and Criminal Investigations / Compliance Actions and Activities / FDA Bioresearch Monitoring Information / Bioresearch Monitoring Program Information

## Bioresearch Monitoring Program Information

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**FDA Bioresearch Monitoring Information**

Bioresearch Monitoring Program Information

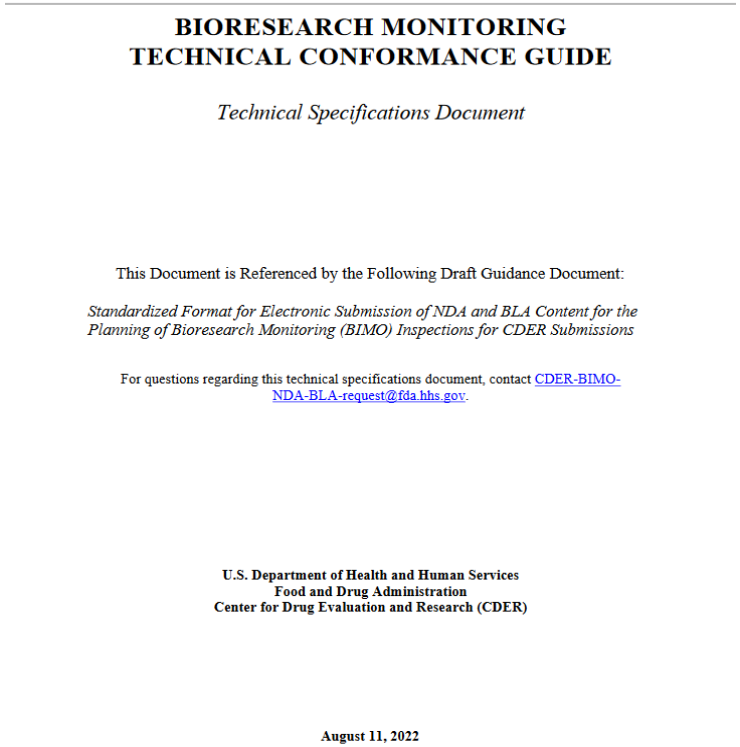
### Program Information

FDA's Bioresearch Monitoring (BIMO) program is a comprehensive program of on-site inspections, data audits, and remote regulatory assessments designed to monitor all aspects of the conduct and reporting of FDA regulated research. The BIMO program was established to assure the quality and integrity of data submitted to the agency in support of new product approvals and marketing applications, as well as, to provide for protection of the rights and welfare of the thousands of human subjects and animals involved in FDA regulated research. It has become a cornerstone of the FDA preapproval process for new medicines, medical devices, food and color additives, veterinary products and, tobacco products introduced to the U.S. consumer.

The BIMO program also takes part in pharmacovigilance activities for postmarketing drug products. These activities serve to detect, understand, and prevent drug-related problems.

# Bioresearch Monitoring (BIMO)

- **BIMO Technical conformance guide**



**BIORESEARCH MONITORING**
**TECHNICAL CONFORMANCE GUIDE**

*Technical Specifications Document*

This Document is Referenced by the Following Draft Guidance Document:

*Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*

For questions regarding this technical specifications document, contact CDER-BIMO-NDA-BLA-request@fda.hhs.gov.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**August 11, 2022**

# Bioresearch Monitoring (BIMO)

- **BIMO submission files**

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267 **Table 1: STF File Tags**

| Requested Item | STF File Tag | Used For | Required File Formats |
|---|---|---|---|
| III.A.*1-2* | data-listing-dataset | General clinical study-level information | .pdf |
| III.A.*3* | Protocol-or-amendment | Protocol and Protocol Amendments, by study | .pdf |
| III.A.*3* | annotated-crf | Sample annotated case report form, by study | .pdf |
| III.B | data-listing-dataset | Data listings, by study (Line listings, by site) | .pdf |
| III.C | data-listing-dataset | Site-level dataset, across studies | .xpt |
| III.C | data-listing-data-definition | Define file | .xml |
| Optional | data-listing-dataset | BIMO Reviewer's Guide | .pdf |

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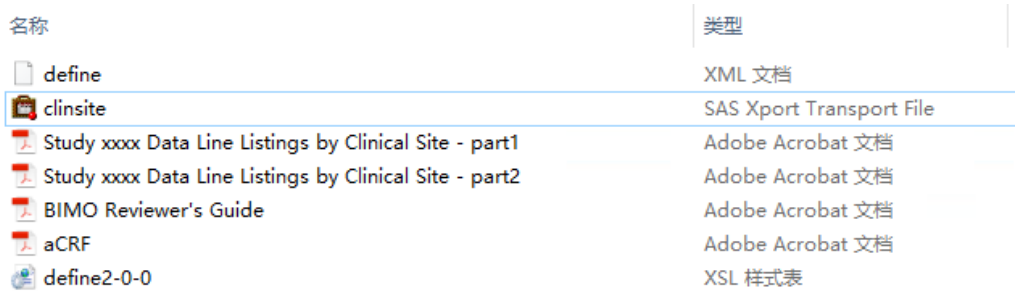
**Provided by clinical operation team**

**Provided by statistical programming team**



# Bioresearch Monitoring (BIMO)

- **Clinsite dataset**

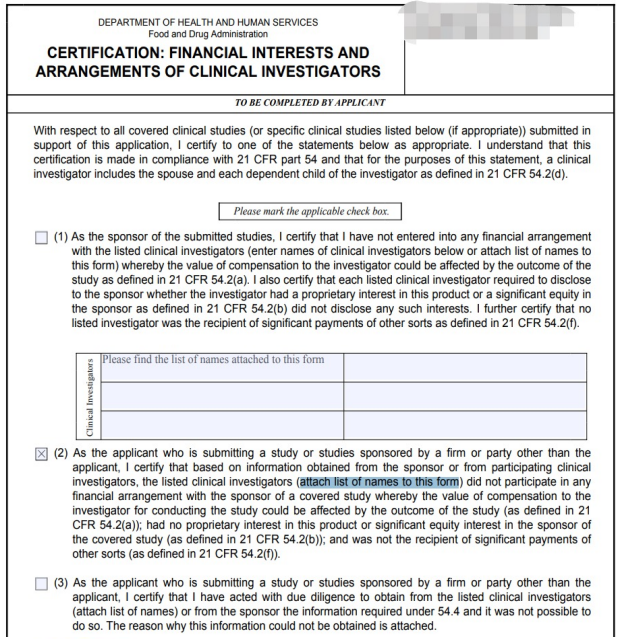
| | STUDYID | TITLE | SPONSOR | IND | NDA | BLA | SITEID | ARM | SAFFOP | ENDPOINT | ENDPTYPE | TRTEFFR | NSAE | SAE | FINLDISC | LASTNAME | FRSTNAME | PHONE | COUNTRY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | xxxx-xxx | A Single-arm, Open-label, Multicenter Phase II Clinical Study of xxxx | xxxx Pharmaceuticals Ltd | 123456 | | 123456 | 01 | xxx | 11 | Objective response rate (ORR) assessed by IRRC per RECIST v1.1 | discrete | 0.3 | 77 | 6 | <$25,000 | XXX | LI | 123456789 | CHN |
| 2 | xxxx-xxx | A Single-arm, Open-label, Multicenter Phase II Clinical Study of xxxx | xxxx Pharmaceuticals Ltd | 123456 | | 123456 | 01 | Screen Failure | 0 | Objective response rate (ORR) assessed by IRRC per RECIST v1.1 | discrete | 0 | 0 | 0 | <$25,000 | XXX | LI | 123456789 | CHN |
| 3 | xxxx-xxx | A Single-arm, Open-label, Multicenter Phase II Clinical Study of xxxx | xxxx Pharmaceuticals Ltd | 123456 | | 123456 | 02 | xxx | 5 | Objective response rate (ORR) assessed by IRRC per RECIST v1.1 | discrete | 0.5 | 41 | 1 | <$25,000 | XXX | WEN | 123456789 | CHN |
| 4 | xxxx-xxx | A Single-arm, Open-label, Multicenter Phase II Clinical Study of xxxx | xxxx Pharmaceuticals Ltd | 123456 | | 123456 | 02 | Screen Failure | 0 | Objective response rate (ORR) assessed by IRRC per RECIST v1.1 | discrete | 0 | 0 | 0 | <$25,000 | XXX | WEN | 123456789 | CHN |
| 5 | xxxx-xxx | A Single-arm, Open-label, Multicenter Phase II Clinical Study of xxxx | xxxx Pharmaceuticals Ltd | 123456 | | 123456 | 03 | xxx | 13 | Objective response rate (ORR) assessed by IRRC per RECIST v1.1 | discrete | 0.4 | 200 | 14 | <$25,000 | XXX | LIU | 123456789 | CHN |
| 6 | xxxx-xxx | A Single-arm, Open-label, Multicenter Phase II Clinical Study of xxxx | xxxx Pharmaceuticals Ltd | 123456 | | 123456 | 03 | Screen Failure | 0 | Objective response rate (ORR) assessed by IRRC per RECIST v1.1 | discrete | 0 | 0 | 0 | <$25,000 | XXX | LIU | 123456789 | CHN |

**The dataset should contain one record per study, clinical site, and treatment arm, and primary endpoint, for the intent-to-treat (ITT) population. Clinical sites included in multiple studies will have separate records for each study.**

# Bioresearch Monitoring (BIMO)

- **Response required**

1) Clarify the discrepancy between the principle investigators' names as reported in clinsite and Module 1.3.4 for Sites xxx and xxx.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

**CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS**

*TO BE COMPLETED BY APPLICANT*

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

*Please mark the applicable check box.*

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| Clinical Investigators | |
|---|---|
| Please find the list of names attached to this form | |
| | |
| | |

☒ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

**APPENDIX 1: CLINICAL STUDY-LEVEL INFORMATION**

*Format for comprehensive and readily located list of all clinical sites that participated in each clinical study. A separate table should be provided for each clinical study.*

**Table A: Format for Clinical Site Lists**

| **Protocol Number: Protocol Title** | | | |
|---|---|---|---|
| **Site Identifier** | **Investigator Name (Prior Clinical Investigator(s))** | **Site Address at Time of Clinical Study (Updated Site Address when exists and available)** | **Site Contact Information at Time of Clinical Study (Updated Contact Information when exists and available)** |
| **SITEID** | **LASTNAME, FRSTNAME, MINITIAL** | **FACILITY NAME STREET CITY, STATE, POSTAL COUNTRY** | **PHONE FAX EMAIL** |
| 0001* | Doe, John M. | Doe University Department of Medicine<br>1 Main St., Suite 100<br>Silver Spring, MD 20850<br>USA | Phone: 1-555-555-5555<br>Fax: 1-555-555-5555<br>Email:<br>john.doe@mail.com |
| 0002 | Doe, Jean<br>(Smith, John) | Doe University Department of Medicine<br>1 Main St., Suite 100<br>Silver Spring, MD 20850<br>USA | Phone: 1-555-555-5555<br>Fax: 1-555-555-5555<br>Email:<br>john.smith@mail.com<br>(Phone: 1-555-555-5554<br>Email:<br>jean.doe@mail.com ) |
| 003 | Dietric-Fischer, Inge | Hartmannstrasse 7<br>5300 Bonn 1<br>Germany | Phone:49-555-555-5555<br>Fax: 49-555-555-5555<br>Email:<br>Dietric.Fischer@web.de |
| * Site terminated, or clinical investigator changed, at request of sponsor before study completion. | | | |

# Bioresearch Monitoring (BIMO)

- **Response required**

2) Submit a revised clinsite dataset in which the TRTEFFR is consistent with the CSR (denominator limited to the primary efficacy population as assessed by IRRC): i.e., TRTEFFR = total subjid number where AVALC in ("CR","PR") and param="Best Overall Response for FAS per IRRC" in ADaM.ADRS) / (total subjid number where ADaM.ADSL.FIRRCFL=”Y”)

# Bioresearch Monitoring (BIMO)

| Variable Index | Varia |
|---|---|
| 13 | SAFF |
| 14 | SCRI |
| 15 | DISC |
| 16 | DISC |
| 17 | ENDI |
| 18 | ENDI |
| 19 | TRTE |
| 20 | TRTE |

**Revision History**

| Date | Version | Summary of Changes |
|---|---|---|
| 12/28/2017 | 1.0 | Original Version |
| 07/23/2020 | 2.0 | 1. Corrected footnote hyperlinks<br>2. Edited variable names in examples and tables to maintain consistency across document<br>3. Clarified document, listings, and data requests<br>4. Deleted request for SITEFFE and SITEFFS variables in clinsite.xpt<br>5. Added COHORT variable<br>6. Revised PROTVIOL variable to IMPDEV and NOIMPDEV variables<br>7. Provided additional instructions for placement of files per eCTD format |
| 08/11/2022 | 3.0 | 1. Rename BIMO Review Guide to BIMO Data Review Guide<br>2. Renamed TRTEFFR to TRTEFFR1<br>3. Added EFFPOP, TRTEFFR2, and CENSOR2 Variables<br>4. Deleted request for TRTEFFS<br>5. Change instructions for use of ISO codes to use of Geopolitical Entities, Names and Codes (GENC) codelist.<br>6. Minor editorial changes. |

| Sample Value |
|---|
| 20 |
| 100 |
| 5 |
| 10 |
| Average increase in blood pressure |
| Continuous |
| 1.00 |
| 0.065 |

| Variable Index | Variable Name | Variable Label | Type | Controlled Terms or Format | Notes or Description | Sample Value |
|---|---|---|---|---|---|---|
| 19 | ENDPTYPE | Primary Endpoint Type | Char | String | Variable type of the primary endpoint (i.e., "continuous," "discrete," "time to event," or "other"). | Continuous |
| 20 | TRTEFFR1 | Treatment Efficacy Result for SAFPOP | Num | Floating Point | Summary statistic for each primary efficacy endpoint by treatment arm at a given site for subjects in SAFPOP. | 1.00 |
| 21 | TRTEFFR2 | Treatment Efficacy Result for EFFPOP | Num | Floating Point | Summary statistic for each primary efficacy endpoint by treatment arm at a given site for subjects in EFFPOP. | 0.98 |

# AOM – Datasets walkthrough meeting

- **Application orientation meeting (AOM)**
  - ✓ Optional but standard in Oncology (especially for Priority, Breakthrough and expedited review applications)
  - ✓ Hear about an application and know applicant's position
  - ✓ requested and held within 45 days of submission
  - ✓ Very little time to prepare
  - ✓ Two-part meeting
    - ➢ one-hour meeting (35-40 mins presentation and 20-25 mins Q&A)
    - ➢ **technical walkthrough - datasets walkthrough meeting (30 minutes)**

# AOM – Datasets walkthrough meeting

- **Datasets walkthrough meeting attendees**

| Sponsor Team | FDA Team |
|---|---|
| Clinical leader and other clinical team members | FDA Clinical Reviewers |
| Regulatory team | |
| Statistical leaders and study statisticians | |
| Statistical programming leader and programmers | FDA Statistical reviewers |
| Clinical pharmacology team members | FDA Clinical Pharmacology reviewers |
| Global medical safety team members | |

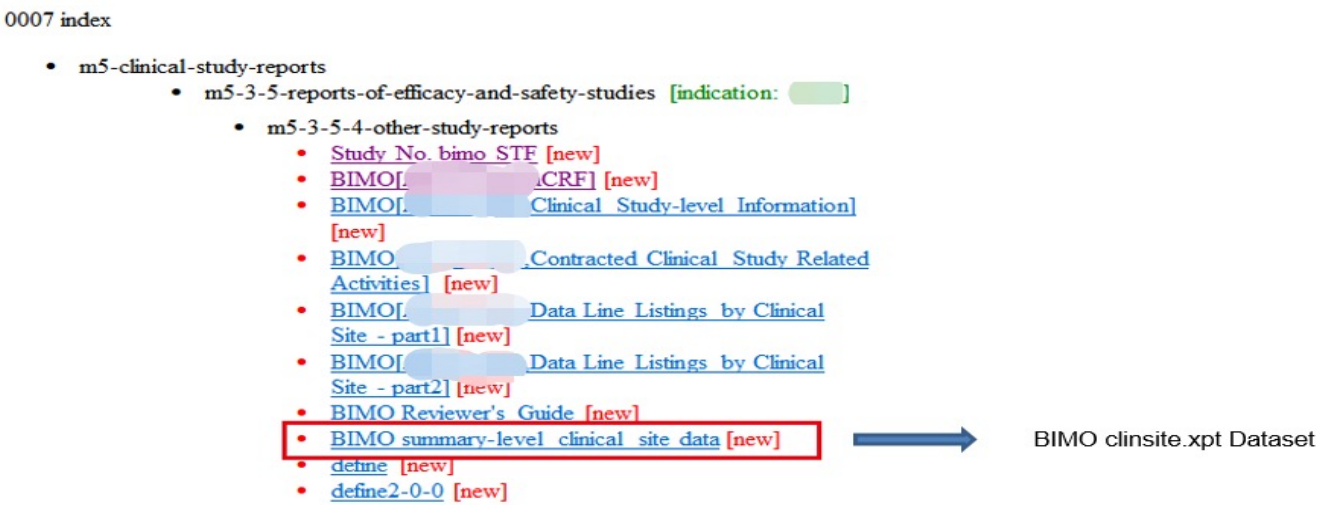
# AOM – Datasets walkthrough meeting

- **Datasets walkthrough meeting presentation preparation**
  - ✓ eCTD overview: show each sequence numbers for the submitted datasets

12 package submitted to FDA including Module1 - Module 5 documentations and updated files per agency comments.

# AOM – Datasets walkthrough meeting

- **Datasets walkthrough meeting presentation preparation**
  - ✓ eCTD index.xml: Point out important submitted datasets (initial submission)



# AOM – Datasets walkthrough meeting

- **Datasets walkthrough meeting presentation preparation**
  - ✓ eCTD index.xml: Point out important submitted datasets (updated submission)

# AOM – Datasets walkthrough meeting

- **Datasets walkthrough meeting presentation preparation**
  - ✓ Key ADaM datasets walkthrough – ADSL：important population flag

## Key ADaM datasets - ADSL

**Key analysis set flag variables:**

| Variable Name | Label |
|---|---|
| SAFFL | Safety analysis set Flag |
| FASINVFL | FAS per Investigator Flag |
| FIRRCFL | FAS per IRRC Flag |

**FASINVFL and FIRRCFL are used to flag Primary efficacy analysis set described in clinical study report and 2.7.3 Summary of Clinical Efficacy**

# AOM – Datasets walkthrough meeting

- **Datasets walkthrough meeting presentation preparation**
  - ✓ Key ADaM datasets walkthrough - efficacy

## Key ADaM datasets - efficacy (ADRS)

**ADRS:** One record per subject per analysis parameter per analysis timepoint. (Basic Data Structure)

**Below parameters are derived in ADRS:**

| ADRS.PARAM | ADRS.PARAMCD |
|---|---|
| Overall Response for FAS per IRRC | IRRCRESP |
| Overall Response for FAS per Investigator | OVRLRESP |
| Best Overall Response for FAS per IRRC | BSTRESIR |
| Best Overall Response for FAS per Investigator | BSTRESIN |

Below date variables can be used to generate DoR/PFS in ADTTE:
DTFTRSP1: Date of First Response per Investigator
DTFTRSP2: Date of First Response per IRRC
FPDDT1: Date of Fir Disease Progression per Investigator
FPDDT2: Date of Fir Disease Progression per IRRC

And according to SAP, variables ADSL.DTHDTC & ADSL.NEWATDT(Date of New Anticancer Therapy) will also be used to derive DoR/PFS

# AOM – Datasets walkthrough meeting

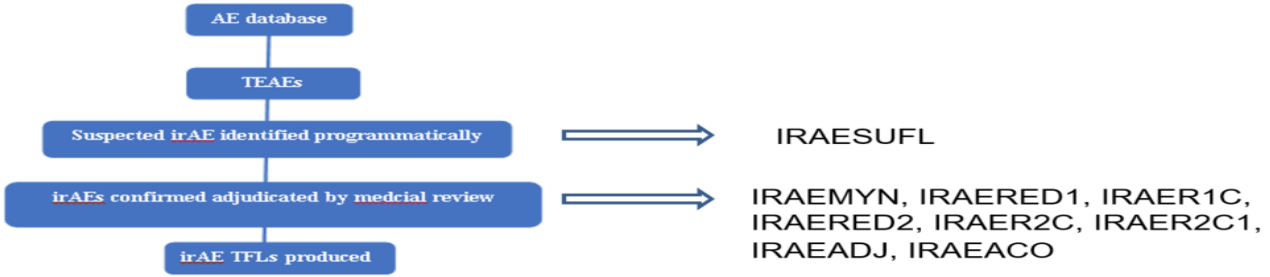
- **Datasets walkthrough meeting presentation preparation**
  - ✓ Key ADaM datasets walkthrough - irAE related analysis

## Key ADaM datasets - safety (pivotal study )

**ADAE:** One record per subject per Adverse Event. (Occurrence Data Structure)

Note: if CTCAE grade of AE change, variables AECTGR1-AECTGR8 used to collect.

**irAE related variables:**



# AOM – Datasets walkthrough meeting

- **Datasets walkthrough meeting presentation preparation**
  - ✓ Key ADaM datasets walkthrough - irAE related analysis

## Key ADaM datasets - safety (pivotal study)

**ADAE.irAEHCAT, irAECAT**

Table 14.3.1.4.1 Time to onset of first irAE and time to resolution - Subjects with irAE - Safety Analysis Set

| irAE Category<br>irAE Subcategory | Total (N=[redacted]) |
|---|---|
| With at Least One irAE (%) | |
| Lung toxicity (pneumonia) | |
| Lung toxicity (pneumonia) | |
| Time to first irAE (Months) [a] | |
| n (%) | |
| Mean (SD) | |
| Median (Min - Max) | |
| Time to resolution (Months) [b] | |
| n (%) | |
| Mean (SD) | |
| Median (Min - Max) | |
| Kaplan Meier Median and 95% CI | |

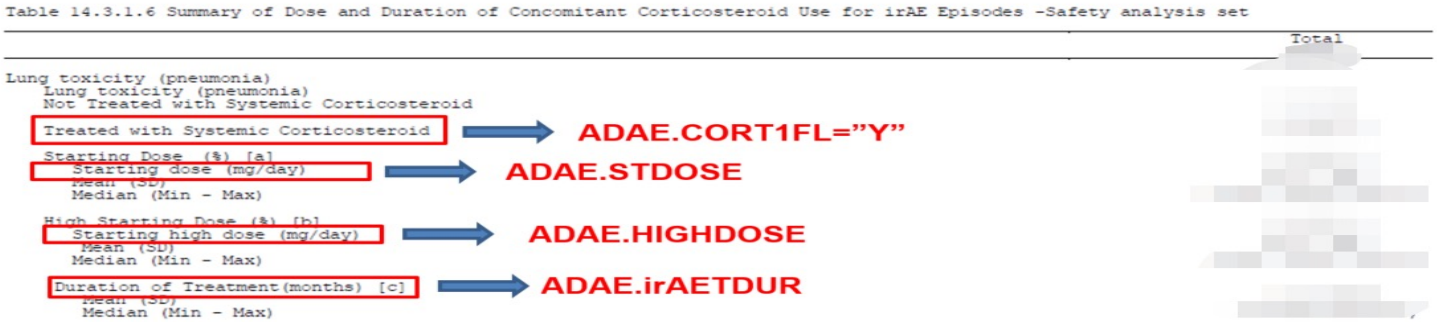
**select records where ADAE.ANL01FL="Y" and then use variable astdy to do descriptive analysis**

**where ADTTE.PARAMCD='IRAETTR'**

# AOM – Datasets walkthrough meeting

- **Dataset walkthrough meeting presentation preparation**
  - ✓ Key ADaM datasets walkthrough - irAE related analysis

## Key ADaM datasets - safety (pivotal study)



# 90-day safety update report

| | Pivotal study | ISS | Label |
|---|---|---|---|
| SDTM | All datasets and define package | Other supportive studies have sufficient treatment exposure and no more patients were dosed after DCO for initial BLA submission, therefore, no safety updates were provided for those studies | FDA's reply:"With regard to the 90-day safety, xxx's proposal not to update the label is likely acceptable but pending FDA's review of the safety data." |
| ADaM | ADSL, ADAE, ADCM, ADLB and define package | | |
| TFLs | No more patients for pivotal study were dosed after DCO for initial BLA submission and There is only one new SAE, no ≥ Grade 3 irAE judged by investigator, and no Grade 5 AE since initial BLA submission, so the Sponsor provide below TFLs in safety update report：<br>Table 1: Summary of TEAE<br>Listing 1: All new or updated AEs and newly added suspected irAEs (after initial BLA submission)<br>Listing 2: Laboratory Assessment (for newly added ≥ Grade 3 lab abnormality)<br>Narratives: Narrative of the new or updated SAE from pivotal study xxx will be submitted | | |

**Lifecycle management: RA may confirmed with Lead statistician/programmer which attributes should be used for submission files, "replace" or "new". We generally should suggest to use "replace".**

# efficacy update and mature DoR update

| | efficacy update | mature DoR update (PMC required) |
|---|---|---|
| SDTM | All datasets and define package (no need to submit again and state in the cover letter that: SDTM datasets used is the same as 90-day safety update) | All datasets and define package |
| ADaM | ADSLxx, ADRSxx, ADTTExx and define package | ADSLxx, ADRSxx, ADTTExx and define package |
| TFLs | Table 14.XX Summary of Time to Response (TTR) and Duration of Response (DoR) Based on RECIST 1.1<br><br>Figure 14.XX Swimmer Plot of Duration of Treatment Based on RECIST 1.1 per IRRC – Full Analysis Set - Responders | Table 14.XX Summary of Time to Response (TTR) and Duration of Response (DoR) Based on RECIST 1.1<br><br>Figure 14.XX Swimmer Plot of Duration of Treatment Based on RECIST 1.1 per IRRC – Full Analysis Set - Responders |

**PMC required description: submit mature duration of response (DOR) results from Trial xxx for the xx responders based on the original data cut-off date for the BLA. Follow all responders for at least 24 months from the date of initial response or onset of disease progression, whichever occurs first.**

# United States Prescribing Information

- **Response required**

FDA ask sponsor to provide the algorithm and SAS program used to determine the select laboratory abnormalities values in Table 3 of the xxx labeling.

**Table 3. Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received XXX in Study XXX**

| Laboratory Abnormality | XXX | |
|---|---|---|
| | All Grades* (%) | Grade 3 or 4* (%) |
| **Chemistry** | | |
| Decreased phosphate | XX | X |
| Decreased sodium | XX | X |
| Increased triglycerides | XX | X.X |
| Increased gamma-glutamyl transferase | XX | X |
| **Hematology** | | |
| Decreased lymphocytes | XX | XX |
| Decreased hemoglobin | XX | X.X |

Toxicity graded according to NCI CTCAE version 4.03.
* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: XX (range of the patient number:XXX to XXX).

**FDA may update USPI's results based on results summarized by themselves. Sponsor's statistical team may reject the updates / comments and provide the correct results based on the results confirmed by SAS program.**

cdisc

# Thank You!