User Guide - Shiny App for General and RECIST checks

The BICR (Blinded Independent Central Review) Data Check Shiny App is intended to be used by solid tumor or hematology DSS teams to explore the data quality of BICR datasets, supporting statistical data review described in Review of BICR Imaging Data in Oncology - Guiding Principles and Good Practices Version 1.0.

The app is built for exploratory purpose. Please review the data check results before making decisions.

Any study specific data check not covered by this app should be programmed by the study teams.

Note: The app title has been renamed from “IRF/IRC Data Checks” to “BICR Data Checks” to align with the standard term recommended by MICR.

Introduction

The BICR Data Check Shiny App and GitLab is intended to be used by oncology study teams in DSS to review BICR data quality and accelerate turnaround for data issue communication. Previous version that works with entimice data can be found at here.

The app can be used for either solid tumor or hematology studies, providing variable checks, between-transfer checks, time point response checks, and general consistency checks.

Term	Description
BICR	Blinded Independent Central Review. Although BICR data can be used interchangeably with IRF data or IRC data, BICR is the standard term recommended by MICR from now on.
IRF	Image Review Form - Form that digitally captures the central assessment facilitated by a system that controls the data presented for the Independent Read
IRC	Independent Read Committee - A committee of imaging experts with defined roles and responsibilities who together accomplish a complete independent read of image data and related clinical reference data
INV	Investigator
FFS	File Format Specifications - Document describing the database tables, and the type, format, naming conventions, and transfer mechanisms for files to be delivered to Roche (GDSR FFS templates)
Charter	Independent Read Charter (Charter templates)

Term	Description
Reader	A radiologist or other specialist who is selected to independently assess radiology data as stipulated in the Charter
TPR	Time Point Response
RECIST	Response Evaluation Criteria in Solid Tumors (Guidance paper)
MICR	Medical Imaging in Clinical Research Group (gsite)
DBL	Database Lock

What's in the App?

Below is a summary of what's in the app. Please refer to the "How to Use" sections for details.

- **Variable Checks**
  - Review general data issues, such as missingness, duplicates, invalid dates, tumor locations, and missing readers.
  - Review whether variables in BICR datasets are correctly valued per FFS.
- **Between-Transfer Checks**
  - Compare BICR datasets transferred between different dates.
  - Specifically, the app will detect patients dropped and added between transfers, observations dropped and added between transfers, as well as response categories and acceptance flags modified between transfers.
- **Verify Overall Response**
  - Check whether overall response categories are assigned per RECIST v1.1 or disease recurrence criteria for solid tumor studies.
- **Other Time Point Response (TPR) Checks**
  - **Overall Response Sequence:** For solid tumor studies, overall responses of PR or SD after CR will be flagged as issues. For hematology studies, overall responses of PMR or NMR after CMR will be flagged as issues.
  - **Nodal Target Lesion:** Accepted TRL records with longest perpendicular measurements of 0 mm will be flagged as issues.
  - **Missing Target Lesion:** Any post-baseline visits with incomplete sets of accepted target lesions, compared with the baseline sets, will be flagged as issues.

    - **Target Lesions of NA/NE:** Patients who do not have target lesions based on TRL but having target responses other than ‘NA’ or ‘NE’ based on RSP will be flagged as issues.
    - **New Lesion Consistency:** Inconsistency of accepted new lesions between TRL and RSP by each visit will be flagged as issues.

- **General Consistency Checks**
    - Check whether (1) patient population, (2) set of scans, and (3) visits and dates are consistent between the independent assessor (BICR) and investigator (INV).

What’s NOT in the App?

Any study specific data check not covered by this app should be programmed by the study teams.

- Concordance check of response assessments between the independent assessor and investigator is not included in this app.
- Verifying overall TPR per LUGANO criteria is currently not implemented.

Data Source

- **Variable Checks**
    - Variable checks are performed based on selected raw (unmapped) BICR datasets: **TID, TRL, and RSP**.

- **Between-Transfer Checks**
    - Between-transfer checks are performed based on two sets of raw (unmapped) BICR datasets: **TID, TRL, and RSP** with different transfer dates.

- **Time Point Response (TPR) Criteria Checks**
    - TPR checks are performed by merging selected raw (unmapped) BICR datasets: **TID** (or **TRL**) and **RSP** together.

- **Other Time Point Response (TPR) Checks**
    - TPR sequence checks are performed based on selected raw (unmapped) **RSP** and **TRL** datasets.

- **General Consistency Checks**
    - Patient population consistency check compares patients from **SDTMv.DM** with those from pooled raw (unmapped) BICR datasets: **TID, TRL, and RSP**.

- Scan consistency and visit/date consistency checks are performed based on either **SDTMv.RS** or **ADRS** only. None of the raw BICR datasets are involved. Therefore, the pre-requisite for running these two checks is that BICR data should be already mapped to RS or ADRS.

How to Use: Data Import

First, please enter the path to raw (unmapped) BICR datasets that have been ingested.

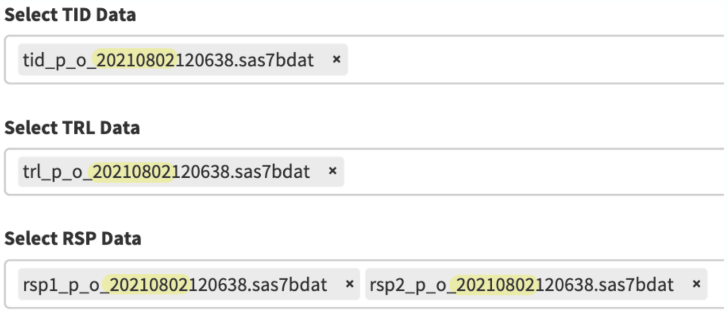
For example, `/ocean/harbour/cdp_testing/eice_share_da/ref/source/noncrf`.

Importing an unextracted zip file is not supported by the app.

After pushing the submit button, you can browse TID, TRL, and RSP datasets located under the path you specified.

Please select datasets with the same data transfer dates here. By default, the latest transfers are selected.

If needed, you can import multiple TID, TRL, or RSP datasets. For example, some studies have multiple RSP datasets (e.g. RSP1 and RSP2). You can choose as many datasets as needed from the selection box.



How to Use: Variable Checks

General Variable Checks

"General Variable Checks" provide DSS teams an option to double check some of the conformance checks performed by DAS, so DSS teams can skip "General Variable Checks" as needed. However, "General Variable Checks" can be more flexible than the conformance checks. For example, you can customize the key variables to define duplicated records, and you can customize the cut-off date to flag invalid future or past records.

- Missing Values
  - Please refer to the study FFS while performing this check. If FFS states "Do not leave blank" for a variable, then missing values should not be expected. This check should be already completed by the DAS team, so the app provides an option to confirm the conformance checks.

- Definition of missing value: empty string `""`, string with a space `" "`, and string with a period `"."` are considered missing values by this app.
- If the character `"NA"` is considered as a missing value in the data, you can click on the check box “Is character”NA” considered missing value?“. The app will then count character `"NA"` as missing values.
- Number and percent of missing values will be displayed for any variable containing missingness.
- To view detailed listings of missing data, you can use the bottom box “Review BICR Data” and choose `Missing` from any variable of interest in the filtering box located at the top of the data table.

- Duplicates
  - KEY variables should specified in the “FIELD #” column of “Data Record Specifications” tables in the FFS. Please review the FFS before making selection. Checking duplicates defined by KEYs per FFS may be already completed by the DAS team, so the app provides an option to confirm the conformance checks.
  - **Or you can also choose any customized KEY variables to serve a specific purpose**. For example, if multiple readers are present, selecting RSP and choosing `PATNUM`, `VISIT`, `RSPD`, `RSCAT`, `RSTESTCD`, and `RSACPTFL` (or `RSPACTFL`) as key variables helps to review any records accepted by none of readers.

  - An example of how to use this check is available in the demo slide here.

FIELD #	VARIABLE NAME	VARIABLE LABEL/ DESCRIPTION	FORMAT SPECIFICATION *	STUDY SPECIFIC INFORMATION
5	TIDD	**Date of Scan** Date at which the scan was taken at the site. **Do not leave blank**	$11 YYYYMMDD	e.g. 20120720
6 KEY	TULNKID	**Link ID** Identifier used to link identified tumors to the assessment results (in TRL dataset) over the course of the study. Each value will be present once per subject in the dataset in association with the specific date/visit at which the tumor was identified. **Do not leave blank**	$40	Please refer to APPENDIX for list of codes

- Invalid Dates
  - You can check for invalid dates, including invalid future dates or invalid past dates. Any observation prior to or beyond any user-defined cutoff date will be returned.

- Scan Dates
    - `TID.VISIT` and `TID.TIDD` should be uniquely corresponded: on a subject level, one visit should not correspond to multiple scan dates, and one scan date should not correspond to multiple visits. If issues are identified, please discuss with the study team to assess if the inconsistency is permitted.

- Tumor Locations
    - Unique values of `TID.TULOC` will be returned.
    - Please refer to "Appendix B - TID DATASET: CONTROLLED TERMINOLOGY" section of the FFS to review if `TID.TULOC` is correctly valued.

- Missing Readers
    - If more than one readers is expected, the output returns any visit assessment (unique by `PATNUM`, `RSPD`, `RSCAT`, and `RSTESTCD`) having only one reader.

Review BICR Data

To review BICR data, please refer to controlled terminologies specified in the appendices of the FFS.

You can apply filters from the boxes located at the top of the data table to identify any variables not conforming with the controlled terminologies. An example of how to use this check is available in the demo slide here.

To allow for faster processing of filters, the report downloaded from this section is currently limited to only 50 rows. You can click on the next page to download another 50 rows.

How to Use: Between-Transfer Checks

Between-transfer check is an optional check to monitor changes between two IRF data transfers. By default, the **second latest** transfers will be selected.

The app can detect the following changes between the current and a previous transfers:

- Patients dropped and added
- Observations dropped and added
- Response (`RSP.RSPRESC`) and RSP Acceptance Flag (`RSP.RSACPTFL`) modified

Patients/observations added are usually expected between transfers, but patients/observations dropped may indicate issues with the transfers.

For the same patient and same visit, modifications of the response categories between transers may be permitted. Please consult with the study team/vendor to confirm if the modifications are justified.

How to Use: Verify Overall Response

This check verifies whether the overall response at each timepoint for each patients is assigned correctly based on the criterion selected by the user on the left-side settings.

Based on the charter, please select *"How is overall response assigned?"*.

Option 1 *"Based on target, non-target, and new lesions (RECIST v1.1)"* and Option 2 *"Based on non-target and new lesions only (RECIST v1.1)"* refer to Table 1 and Table 2 of Standard RECIST v1.1 criteria respectively:

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

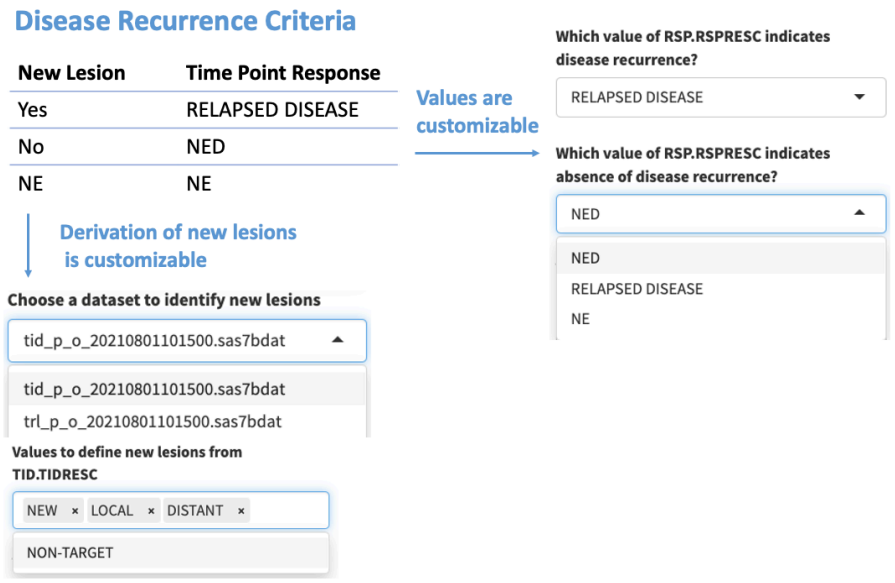
Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Option 3 *"Based on new lesions only (Disease Recurrence)"* refers to customizable disease recurrence criteria:



To perform 'Verify Overall Response', you will need to select a dataset from RSP, TRL, or TID to identify new lesions.

By default, the app assumes that new lesions can be derived from the RSP dataset. If `RSP.RSTESTCD = "NEWLIND"` is available in RSP, selecting RSP as the source to identify new lesions is recommended.

You are also encouraged to select TRL as the source to identify new lesions. In general, selecting RSP or TRL as the source for new lesions should result in the same findings; if not, there may be some inconsistency between TRL and RSP on new lesion identifications. **You can further check the consistency of new lesions between TRL and RSP in the "Other TPR Checks" section.**

Selecting TID as the source to identify new lesions is likely to result in false positive findings - for more details, please see the "Clarification #1" section below.

You can choose not to use RSP as the source for new lesions by clicking the check box *"Click here if you would like to select TRL or TID as the source for new lesion identification."* if you would like to select TRL or TID as the source for new lesions. You will then need to confirm the variables specified in the *"Key variables to left join RSP with TRL (or TID)"* selection box. By default, `STUDYID`, `PATNUM`, and `VISIT` are selected as the merge keys to left join RSP with TRL/TID. Sometimes, adding `Date` as another key may be helpful. For more details, please see the "Clarification #2" section below.

The app re-derives the overall response for each scan and then compares it with the overall response provided by BICR:

When Option 1 *"Based on target, non-target, and new lesions (RECIST v1.1)"* is selected, the app will create and display the following variables as data check results:

- **Target Lesions** is set to values of `RSP.RSPRESC` when `RSP.RSTESTCD = "TRGRESP"`.
- **Non-Target Lesion** is set to values of `RSP.RSPRESC` when `RSP.RSTESTCD = "NTRGRESP"`.
- If RSP is selected as the source for new lesions, **New Lesion** is set to `"Yes"` if `RSP.RSPRESC = "Y"` when `RSP.RSTESTCD = "NEWLIND"`. If TRL or TID is selected as the source for new lesions, **New Lesion** is set to `"Yes"` if `TRL.TRLRESC` or `TID.TIDRESC` is equal to user selected values in *"Values to define new lesions"* and `"No"` otherwise. If the *"Accepted TRL (or TID) records only"* box is checked, TRL (or TID) acceptance flag equal to yes will be applied to find new lesions.
- **Overall Response (BICR)** is set to `RSP.RSPRESC` when `RSP.RSTESTCD = "OVRLRESP"`. If the *"Accepted RSP records only"* box is checked, RSP acceptance flag equal to yes will be applied return accepted RSP records only.

- **Overall Response (App)** is automatically derived by this app based on **Target Lesion**, **Non-Target Lesion**, and **New Lesion** per RECIST v1.1.
- **Issue Flag** is set to `"Y"` if `Overall Response (BICR)` is different from `Overall Response (App)` and `"N"` otherwise.

When Option 2 *"Based on non-target and new lesions only (RECIST v1.1)"* is selected, the app will create and display the following variables as data check results:

- **Non-Target Lesion** is set to values of `RSP.RSPRESC` when `RSP.RSTESTCD = "NTRGRESP"`.
- If RSP is selected as the source for new lesions, **New Lesion** is set to `"Yes"` if `RSP.RSPRESC = "Y"` when `RSP.RSTESTCD = "NEWLIND"`. If TRL or TID is selected as the source for new lesions, **New Lesion** is set to `"Yes"` if `TRL.TRLRESC` or `TID.TIDRESC` is equal to user selected values in *"Values to define new lesions"* and `"No"` otherwise. If the *"Accepted TRL (or TID) records only"* box is checked, TRL (or TID) acceptance flag equal to yes will be applied to find new lesions.
- **Overall Response (BICR)** is set to `RSP.RSPRESC` when `RSP.RSTESTCD = "OVRLRESP"`. If the *"Accepted RSP records only"* box is checked, RSP acceptance flag equal to yes will be applied return accepted RSP records only.
- **Overall Response (App)** is automatically derived by this app based on **Non-Target Lesion**, and **New Lesion** per RECIST v1.1.
- **Issue Flag** is set to `"Y"` if `Overall Response (BICR)` is different from `Overall Response (App)` and `"N"` otherwise.

When Option 3 *"Based on new lesions only (Disease Recurrence)"* is selected, the app will create and display the following variables as data check results:

- **New Lesion**: If `TID.TIDRESC` or `TRL.TRLRESC` is equal to user selected values in *"Values to define new lesions"*, then `New Lesion = "Yes"`. If `TID.TIDRESC = "NE"` or `TRL.TRLRESC = "NE"`, then `New Lesion = "NE"`. Otherwise, `New Lesion = "NO"`. If the *"Accepted TRL (or TID) records only"* box is checked, TRL (or TID) acceptance flag equal to yes will be applied to find new lesions.
- **Overall Response (BICR)** is set to `RSP.RSPRESC` when `RSP.RSTESTCD = "DRCRIND"`. If the *"Accepted RSP records only"* box is checked, RSP acceptance flag equal to yes will be applied return accepted RSP records only.
- **Overall Response (App)** is automatically derived by this app. If `New Lesion = "Yes"` then disease recurs; else if `New Lesion = "NE"` then disease recurrence is not evaluable; else disease does not recur. Users are expected to specify which value of `RSP.RSPRESC` indicates disease recurrence and no disease recurrence to populate this `Overall Response (App)` variable.

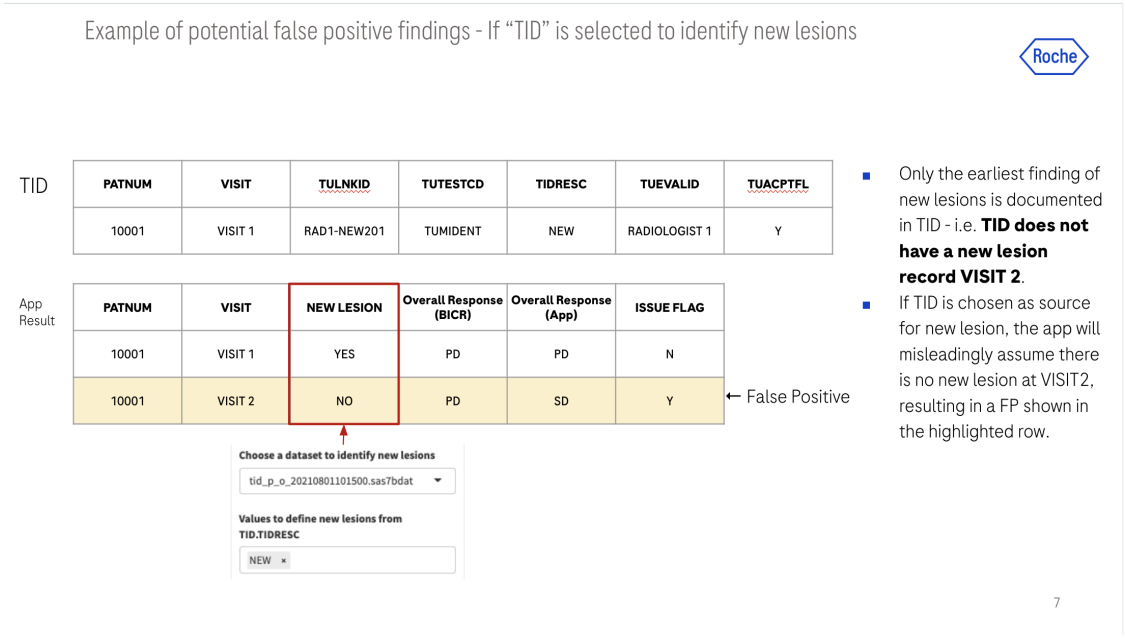
- **Issue Flag** is set to `"Y"` if `Overall Response (BICR)` is different from `Overall Response (App)` and `"N"` otherwise.

You can filter by `Issue Flag = "Y"` from the top of the data table to review overall TPR inconsistent with results derived by the app.

Note: In the latest GDSR standard, the acceptance flags `TID.TIDACTFL`, `TRL.TRLACTFL`, `RSP.RSPACTFL` have been renamed to `TID.TUACPTFL`, `TRL.TRACPTFL`, and `RSP.RSACPTFL` respectively. To avoid confusion, the TPR check function renamed the acceptance flags to `TID Acceptance`, `TRL Acceptance`, and `RSP Acceptance` respectively.

The app's code to automatically derive TPR per RECIST v1.1 or disease recurrence criteria is available in the GitLab repository.

Clarification #1: if TID is selected as the source data to identify new lesions, there may be some false positive findings. The recommended source data for new lesion is TRL or RSP.



Example of potential false positive findings - If "TID" is selected to identify new lesions

TID

PATNUM	VISIT	TULNKID	TUTESTCD	TIDRESC	TUEVALID	TUACPTFL
10001	VISIT 1	RAD1-NEW201	TUMIDENT	NEW	RADIOLOGIST 1	Y

TRL

PATNUM	VISIT	TRLNKID	TRTESTCD	TIDRESC	TUEVALID	TUACPTFL
10001	VISIT 1	RAD1-NEW201	TUMSTATE	PRESENT	RADIOLOGIST 1	Y
10001	**VISIT 2**	**RAD1-NEW201**	**TUMSTATE**	**PRESENT**	**RADIOLOGIST 1**	**Y**

RSP

PATNUM	VISIT	RSTESTCD	RSPRESC	RSEVALID	RSACPTFL
10001	VISIT 1	NEWLIND	PRESENT	RADIOLOGIST 1	Y
10001	**VISIT 2**	**NEWLIND**	**PRESENT**	**RADIOLOGIST 1**	**Y**

App Result

PATNUM	VISIT	NEW LESION	Overall Response (BICR)	Overall Response (App)	ISSUE FLAG
10001	VISIT 1	YES	PD	PD	N
10001	VISIT 2	YES	PD	PD	N

← Correct finding: no issue identified

- **Both TRL and RSP are more robust sources of new lesions.**

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Clarification #2: If you decide to use TRL (or TID) as the source data to identify new lesions, the app findings may differ depending on the choice of key variables to merge TRL/TID with RSP.

App findings may differ depending on the choice of key variables to merge TRL/TID with RSP.

TRL

PATNUM	VISIT	TRLD	TRLNKID	TRTESTCD	TRLRESC
10001	**UNSCH**	**20200101**	RAD1-NEW201	TUMSTATE	NE
10001	**UNSCH**	**20210201**	RAD1-NEW201	TUMSTATE	PRESENT

RSP

PATNUM	VISIT	RSPD	RSTESTCD	RSPRESC
10001	**UNSCH**	**20200101**	OVRLRESP	SD
10001	**UNSCH**	**20210201**	OVRLRESP	PD

- When the same visit label is associated with more than one scan dates, excluding "Date" from the merge keys may result in false positives since merging cannot be handled properly.
- The workaround is to **add "Date"** as one of the key variables for merging:

Key variables to left join RSP with TRL

STUDYID × PATNUM × VISIT × Date ×

Date refers to RSP.RSPD and TRL.TRLD

App result when "Date" is **removed** from the merge keys

PATNUM	VISIT	NEW LESION	Overall Response (BICR)	Overall Response (App)	ISSUE FLAG	TRLD	RSPD
10001	UNSCH	YES	SD	PD	Y	**20200101**	**20210201**

← **False Positive:** If just merging by STUDYID, PATNUM and VISIT, the app cannot handle the merge properly due to conflicting scan dates

App result when "Date" is **added** to the merge keys

PATNUM	VISIT	NEW LESION	Overall Response (BICR)	Overall Response (App)	ISSUE FLAG	DATE
10001	UNSCH	NO	SD	SD	N	**20200101**
10001	UNSCH	YES	PD	PD	N	**20210201**

← **Correct Finding:** this issue can be resolved after adding "Date" to merge keys

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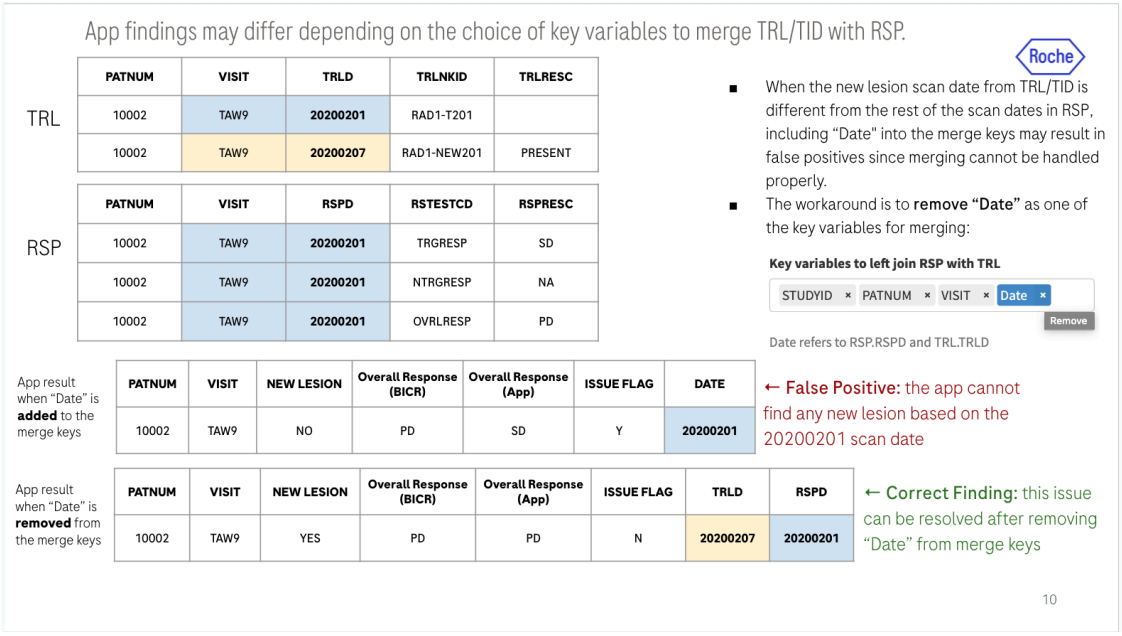
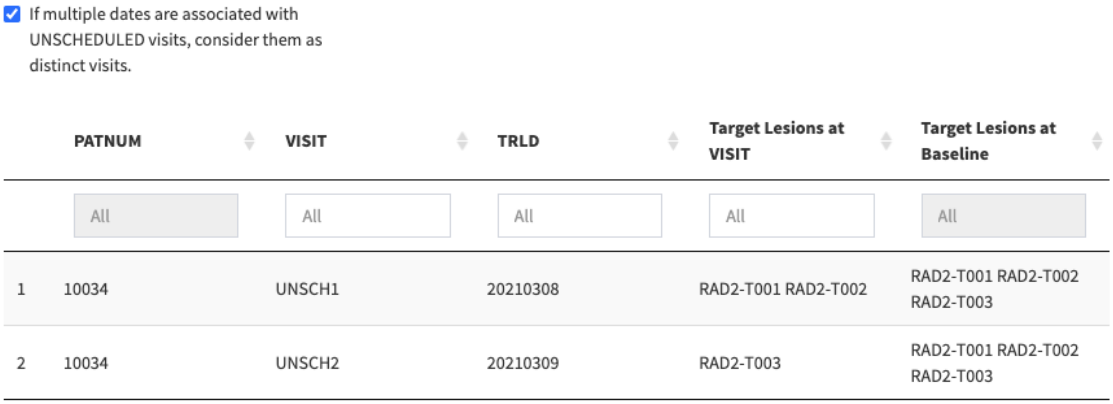


Clarification #3: If the app returns as an issue for 'Overall Response (BICR) = NED' vs. 'Overall Response (App) = NE', please check the study FFS to confirm if NED is permitted.

How to Use: Other Time Point Response (TPR) Checks

- Overall Response Sequence
  - For solid tumor studies, accepted overall responses of PR or SD after CR will be flagged as issues.
  - For hematology studies, accepted overall response of PMR or NMR after CMR (for PET and clinical) or PR or SD after CR (for CT or MRI and clinical) will be flagged as issues.
  - Please refer to the BICR Charter to confirm whether such invalid sequence is considered as an issue.
- Nodal Target Lesion
  - Accepted TRL records with longest perpendicular measurements of 0 mm (i.e., `TRL.TRLRESN = 0` when `TRL.TRTESTCD = 'LPERP'`) will be flagged as issues.
  - Theoretically, nodal target lesions having longest perpendicular measurements of 0 mm are not possible, but they could happen in practice. For example, when lymph nodes completely disappear under detectable limits, they cannot be reliably measured and 0mm could be entered. Please double check with the Charter or the BICR vendor to confirm if these are considered as issues.
- Missing Target Lesion
  - For each patient, the set of accepted target lesions in TRL should be consistent throughout all visits.

- Target lesions based on TRL are defined as `TRL.TRLNKID` containing `-T[digits]`.
- Any post-baseline visits with incomplete sets of accepted target lesions, compared with the baseline sets, will be flagged as issues.
- Baseline visits are defined as `TRL.VISIT = 'SCRN'` or `'SCREENING'`.
- By default, the checkbox *'If multiple dates are associated with UNSCHEDULED visits, consider them as distinct visits'* is clicked, which means that the app considers scans from multiple dates as distinct scans even if they are all labeled as the same unscheduled visit. This option is meaningful for studies that do not differentiate multiple unscheduled visits via `VISIT = 'UNSCH1'`, `VISIT = 'UNSCH2'`, etc..
    - For example, as shown in the example output below, patient 10034 have two scans from `TRLD = '20210308'` and `TRLD = '20210309'`. **Even though these two scans are from the same unscheduled visit (`VISIT = 'UNSCH'`) based the original BICR data, the app recodes them into `VISIT = 'UNSCH1'` and `VISIT = 'UNSCH2'` respectively** because the option *'If multiple dates are associated with UNSCHEDULED visits, consider them as distinct visits'* is selected via the checkbox.
    - If you unclick the checkbox, the app will consider scans from `TRLD = '20210308' & VISIT = 'UNSCH'` and `TRLD = '20210309' & VISIT = 'UNSCH'` as a single time point, and these two visits would not be considered as issues.



If multiple dates are associated with UNSCHEDULED visits, consider them as distinct visits.

	PATNUM	VISIT	TRLD	Target Lesions at VISIT	Target Lesions at Baseline
	All	All	All	All	All
1	10034	UNSCH1	20210308	RAD2-T001 RAD2-T002	RAD2-T001 RAD2-T002 RAD2-T003
2	10034	UNSCH2	20210309	RAD2-T003	RAD2-T001 RAD2-T002 RAD2-T003

- Target Lesions of NA/NE
    - Patients who do not have target lesions based on TRL but having target responses other than `'NA'` or `'NE'` based on RSP (i.e. `RSP.RSPRESC = 'NA'` or `'NE'` when `RSP.RSTESTCD = 'TRGRESP'`) will be flagged as issues.
    - Target lesions based on TRL are defined as `TRL.TRLNKID` containing `-T[digits]`.

- New Lesion Consistency
    - Inconsistency of accepted new lesions between TRL and RSP by each visit will be flagged as issues.
    - New lesions per TRL are defined as `TRL.TRLNKID` containing `'NEW'`.
    - New lesions per RSP are defined as `RSP.RSPRESC = 'Y'` when `RSP.RSTESTCD = 'NEWLIND'`.
    - This check is only applicable for studies having new lesions mapped under RSP (having `RSP.RSTESTCD = 'NEWLIND'`).

How to Use: General Consistency Checks

Patient Population Consistency

Patient population consistency check compares patients from **SDTMv.DM** with those from pooled raw (unmapped) BICR datasets: **TID, TRL, and RSP**.

Scan Consistency

Scan consistency check compares the set of scans from BICR with the one from INV to identify scans unique to BICR and scans unique to INV. Please note that this check is built based on **SDTMv.RS** or **ADRS** (depending on the user's choice) only - i.e., scans for both BICR and INV are extracted from SDTMv.RS or ADRS, and none of the raw BICR datasets are involved. **Therefore, the pre-requisite for running this check is that BICR data should be already mapped to SDTMv.RS or ADRS**.

Visit and Scan Date Consistency

Visit and date consistency checks are performed based on either **SDTMv.RS** or **ADRS** only. None of the raw BICR datasets are involved. **Therefore, the pre-requisite for running this check is that BICR data should be already mapped to SDTMv.RS or ADRS**.

When RS is imported, `"Overall Response"` will be selected by default for *"Please select RS.RSTEST of interest"*, and by default the app will pre-filter accepted responses from BICR before running the check.

When ADRS is imported, `"Overall Response by Investigator"` and `"Overall Response by IRF"` will be selected for *"Please select ADRS.PARAM of interest"*. It may be helpful to switch to parameters `"Best Confirmed Overall Response by Investigator"` and `"Best Confirmed Overall Response by IRF"` as needed.

The app looks for 2 types of inconsistencies:

- 1 VISIT matches multiple DATEs
- 1 DATE matches multiple VISITs

Within these 2 types of inconsistencies, the app further considers 3 scenarios:

- The inconsistency occurs only in BICR data (e.g., for a certain patient, within the BICR subset of SDTMv.RS or ADRS, 1 visit matches multiple response dates or vice versa)
- The inconsistency occurs only in INV data (e.g., for a certain patient, within the INV subset of SDTMv.RS or ADRS, 1 visit matches multiple response dates or vice versa)
- The inconsistency occurs between the INV and BICR data (e.g., for a certain patient, 1 visit in the BICR subset of SDTMv.RS or ADRS matches multiple dates in the INV subset of SDTMV.RS or ADRS or vice versa)

General Consistency vs. Concordance of Response

- General Consistency between BICR and INV
    - Ensuring general consistency of BICR vs. INV data, such as patient population and visit/scan dates consistencies, can potentially prevent discordance of responses and should be reviewed during the conduct of the study until unblinding
    - Implemented by this app
- Direct Comparison between BICR and INV Responses
    - Onco/Heme agreement
        - Assess the **discordance rate** between investigator and central assessment, when sufficient data is available. If deemed too high, investigate discrepant cases further. *Data cleaning is ongoing!*
        - The independent review must remain **independent**
            - Changes to the data need to be justified and documented by the provider
            - Imaging results should **not be shared** from site to BICR and from BICR to site
    - Onco/Heme discussion
        - For some studies (e.g. some heme clinical trials, for response criteria with more complex derivation algorithms), it is recommended to identify and follow-up on the discrepant BICR and investigator imaging responses early during the study conduct, in order to check that the central review does not deviate from the charter/protocol (**first, check that the charter is written in accordance with the protocol**).
            - The clinical scientist and the statistical programmer (with support from the statistician) should agree on *an objective criteria to define theoretically odd cases*. The list of selected patients is then *reviewed by the clinical scientist*.

        - If the BICR response does not deviate from the charter/protocol, then no query is raised to the provider, even if it is different from the investigator response
        - If the BICR response deviates from the charter/protocol, assess whether the response or the charter need to be updated and inform the provider of the finding(s).
    - Example RMarkdown code which knits html report are available

FAQ

- **Who is the intended user of the app?**
    - The app is intended for DSS to perform statistical review of BICR data.
    - Accountable: Statistician
    - Responsible:
        - Statistical Programmer (review of the data/RShiny)
        - DQL or ExBP lead (communication between study team and provider)
        - Service Provider (resolution of findings)
    - Consulted: Clinical Scientist
    - Informed: SLT, GSM

- **When should I use the app?**
    - The statistical review should be performed during the conduct of the study (draft transfers) and at the time of database lock for a reporting event (draft transfer), prior to the final transfer.

- **What's the difference between DAS conformance checks and variable checks?**
    - The DAS conformance check focuses on the compliance of basic variable formats, such as variable name, label and length.
    - The variable check allows users to review whether values of the variables are populated following the controlled terminologies specified in the FFS.

- **Why do we verify overall responses in solid tumor studies?**
    - In solid tumor studies, overall responses can be 1) selected by the BICR system per RECIST v1.1 criteria and then reviewed by the readers - readers can overwrite the system-derived overall responses providing comments 2) entirely assigned by the readers based on RECIST v1.1 or disease recurrence criteria.

    - Team should review any overall responses not following the RECIST v1.1 or disease recurrence criteria.

- **Which version of the RECIST criteria does this app use for 'Verify Overall Responses'?**
    - The app has a built-in function (see GitLab repository) to implement Table 1 and Table 2 of the standard RECIST v1.1 criteria guidance paper.

- **Why is the raw BICR data (prior to mapping to SDTMv) the preferred data source used in this app?**
    - Raw BICR datasets (TID, TRL, and RSP) always come before mapping to SDTMv. Study teams can run this app as soon as they receive any draft transfers from the IRC.
    - Identifying data issues on the raw data level can make the communication with the independent read vendor easier.

- **Why are the scan consistency check and visit/date consistency check based on SDTMv/ADaM only, instead of comparing raw BICR datasets with STDMv/ADaM?**
    - Visit code lists can be different between BICR datasets and INV datasets, making it difficult to merge BICR datasets with INV datasets by visit in the app.

    - If both BICR and INV responses are mapped to the RS domain, you can select importing RS to perform the check. The app uses `RS.RSEVAL = "INDEPENDENT ASSESSOR"` vs. `RS.RSEVAL = "INVESTIGATOR"` to compare the visit and dates between BICR and INV.
    - Else, you can choose to perform the check based on ADRS. The app then uses `ADRS.PARCAT2` to distinguish the BICR visit and dates from the INV visit and dates.

Changelog

- Entimice data support has been removed. Ocean is supported.
- Code repo migration (2023-11-20)
    - Code repository has been migrated from GitHub to GitLab. All links referring to GitHub have been replaced by GitLab links in both the app and the user guide.
- Hotfix (2023-11-03)
    - The app has been redeployed to fix a bug in "Missing Target Lesion" check.
- **Major update: Version 0.1.1 (2023-08-15)**

- **General Updates**
    - Help text throughout the app has been updated to provide better clarification.
- **Updates in “Time Point Response Check”**
    - The tab “TPR Criteria Checks” has been renamed as “Verify Overall Response”.
    - The tab “TPR Sequence Checks” has been renamed as “Other TPR Checks”, with the following four new checks added to the tab:
        - Nodal Target Lesion: Accepted TRL records with longest perpendicular measurements of 0 mm will be flagged as issues.
        - Missing Target Lesion: Any post-baseline visits with incomplete sets of accepted target lesions, compared with the baseline sets, will be flagged as issues.
        - Target Lesions of NA/NE: Patients who do not have target lesions based on TRL but having target responses other than ‘NA’ or ‘NE’ based on RSP will be flagged as issues.
        - New Lesion Consistency: Inconsistency of accepted new lesions between TRL and RSP by each visit will be flagged as issues.
- **Updates in “General Variable Check”**
    - Clarifications have been added within the app and to the user guide.
    - For “Review BICR Data”, users can now download up to 50 records at a time instead of just 10 records.
- **Updates in “General Consistency Checks”**
    - For “Visit and Scan Date Consistency”, when RS is imported, “Overall Response” is now selected by default for “Please select RS.RSTEST of interest”. When ADRS is imported, “Overall Response by Investigator” and “Overall Response by IRF” are now selected for “Please select ADRS.PARAM of interest”.
    - For “Visit and Scan Date Consistency” and when RS is imported, by default the app pre-filters accepted responses from BICR before running the check.

- Hotfix (2023-07-17)
    - ‘Time Point Response’ checks have been updated so that these checks can be run for BICR data without acceptance flags.

- Hotfix (2023-07-10)
    - Except for “Review BICR Data”, reverted to user-side processing for `DataTables` to fix the downloading issue.
- Version 0.1.0 (2023-06-08)
    - **Updates in “Variable Check”**
        - For the “Invalid Dates” check, users can now specify a direction, either before or after a specified date, to identify invalid past or future dates. Any observations prior to or beyond the selected cutoff date will be returned.
        - Server-side processing has been enabled for all `DataTables` in this Shiny app, which significantly increases the processing speed when using the “Review BICR Data” section.
    - **Updates in “Between-Transfer Check”**
        - Users can now specify which variables to keep in the app findings via the “Variables to display in the listing below” selection box.
        - Under “List of Response Modified”, the RSP acceptance flag (`RSP.RSACPTFL` per latest GDSR standard or `RSP.RSPACTFL` per previous GDSR standard) can now be reviewed along with the changes in responses. If the app detects a change in the acceptance flag (e.g. from `"Y"` to `"N"` or vice versa) for the same `PATNUM`, `VISIT`, `RSPD`, `RSTESTCD`, and `RSEVALID` between the transfers being compared, `RSACPTFL.Latest` and `RSACPTFL.Previous` will be included in the app findings together with `RSPRESC.Latest` and `RSPRESC.Previous`.
    - **Updates in “Time Point Response Check”**
        - For “TPR Criteria Checks”, users need to select the source data to identify new lesions so that the app can use this information to verify the overall responses. Previously, only TRL and TID were supported as the options for new lesion source, but now RSP is supported as another option and RSP has been set as the default option. To learn more about this update, please refer to the “How to Use: Time Point Response (TPR) Criteria Checks” section in this User Guide.
        - If users select TRL or TID as the source data for new lesions, the app re-derives the overall responses after merging TRL or TID (for new lesions) with RSP (for target and non-target lesions) by variables specified in the “Key variables to left join RSP with TRL” selection box. Previously, the default keys were `STUDYID`, `PATNUM`,

`Date` (referring to `RSPD`, `TRLD`, or `TIDD`), and `VISIT`, but now the default keys are just `STUDYID`, `PATNUM`, and `VISIT`. For recommendations on how to set the key variables, please read the "Clarification #2" section under "How to Use: Time Point Response (TPR) Criteria Checks" in this User Guide.

        - We have fixed bugs to resolve false positives when TRL is selected as the source data for new lesions. Using TID as the source data for new lesions may still result in some false positives, and please refer to the "Clarification #1" section under "How to Use: Time Point Response (TPR) Criteria Checks" in the User Guide for more details.
        - The term "time point response" or "TPR" has now been replaced by "overall response" when it is actually referring to "overall response".
    - **Updates in "General Consistency Check"**
        - A new check - "Check consistency of scans between INV and BICR" has been added under the "General Consistency Check" tab. It identifies scans unique to BICR and scans unique to INV based on the RS domain or the ADRS dataset. For more details, please refer to the notes on "Scan consistency" under "How to Use: General Consistency Checks" in this User Guide.
- Version 0.0.9.1 (2022-05-02)
    - Users can now customize key variables in the "Missing Readers" check (previously, keys are hard coded as PATNUM, RSPD, RSCAT, and RSTESTCD).
- Version 0.0.9 (2022-03-29)
    - Bug fixes in TPR criteria checks: when TRL is used to find new lesions, the app now pre-filters TRL.TRLRESC by TRL.TRLNKID containing "NEW".
    - Minor UI enhancements
- Version 0.0.8.1 (2022-02-18)
    - `" "`, `""`, and `"."` are now displayed as `"Missing"` instead of `NA` in the app.
    - Time Point Response Check:
        - When clicking on "Accepted TID/TRL records only", the app will no longer filter by acceptance flag of yes in the output. That is, all TID/TRL records, regardless of acceptance status, will be shown in the output. If the checkbox is clicked, accepted TID/TRL records will be used to define new lesions.

        - Showing distinct records by variable displayed is now a new feature.
- Version 0.0.8 (2022-02-02)
    - NEW check added: TPR sequence checks have been added for both solid tumor and hematology studies.
        - For solid tumor studies, overall response of PR or SD after CR will be flagged as issues.
        - For hematology studies, overall response of PMR or NMR after CMR will be flagged as issues.
    - “Cross Transfer Check” has been renamed to “Between-Transfer Check” to avoid confusion.
        - “Between-Transfer Check” compares latest set of BICR data with any user-selected prior set.
    - Multi-file comparison is now supported in “Between-Transfer Check”.
        - E.g. If a study has more than one RSP datasets (RSP1 and RSP2), you can now compare latest RSP1 with previous RSP1 and latest RSP2 with previous RSP2 at the same time.
    - In “General Consistency Check”, ADRS.ADT is now used for date vs. visit checks instead of ADRS.RSDTC.
    - In “General Consistency Check”, you can now pre-specify RS.RSTEST before running date vs. visit checks.
- Version 0.0.7 (2022-01-04)
    - Fixed bug when counting unique patients from pooled BICR datasets.
    - Fixed bug in cross transfer check: default keys are now used to identify observations added or dropped.
    - Updated link to Review of BICR Imaging Data in Oncology - Guiding Principles and Good Practices Version 1.0
- Version 0.0.6 (2021-10-22)
    - App title has been renamed from “IRF/IRC Data Checks” to “BICR Data Checks” to align with the standard term recommended by MICR.
- Version 0.0.5 (2021-09-24)
    - Fixed bug in cross transfer check: Previous release had false negative regarding patient dropped, which has been resolved in version 0.0.5.
    - Fixed bug time point response check: When target lesion is CR, non-target lesion is NA, new lesion is NO, TPR should be CR

    - Enhanced time point response check: If available, evaluator ID has been added to key variables to transpose RSP
- Version 0.0.4 (2021-09-10)
    - In the time point response check section, the app is now able to handle RSGRPID if both global review and timepoint review are included in RSP.
    - Updated link to the example concordance check R Markdown code.
    - Fixed report downloading issue - now all rows of the table can be downloaded at once.
    - `clear_cache = FALSE` has been added to `rice::rice_read()`.
- Version 0.0.3 (2021-09-02)
    - In the general consistency check section, if ADRS is selected to check visit and data consistency, users can pre-specify values of ADRS.PARAM of interest before running the check.
    - In the time point response check section, summary of TPR check is now available.
    - In the time point response check section, more error catchings are added to improve the robustness.
- Version 0.0.2 (2021-08-27)
    - In the general consistency check section, in addition to the RS domain, importing ADRS is now supported to perform the date and visit consistency check.
    - In the time point response check section, users can now select either TID or TRL to derive new lesions.
    - In the time point response check section, the choices in the “Variables to display in the output” selection box are now dynamic.
    - `ricepass` is used for secure login to entimICE.
    - Multiple bugs have been fixed.
    - User guide has been updated.
- Version 0.0.1 (2021-08-16)
    - Initial release

Getting Help

For any questions, please open issues on BICR Data Check repo for help.

Useful Links

- Review of BICR Imaging Data in Oncology - Guiding Principles and Good Practices Version 1.0
- BICR App Demo Slides
- GDSR FFS Templates

    - Solid tumor: STA (Solid Tumor Assessments); STA_ATS (Solid Tumor Assessments Adjuvant Therapy Setting)
    - Hematology: LYMPH_PETCT (Lymphoma Radiologic and Positron Emission Tomography Assessments)

- RECIST v1.1 Guidance Paper
- Working Guidance for IRF Data Quality Control in Atezolizumab Studies (You may need to request for access to view this document.)
- Clinical Trial Imaging Endpoint Process Standards Guidance for Industry
- Non-CRF Data Wiki
- sdtmchecks App
- MICR gsite
- App demo recording - Yinqi's intern exist presentation

App Team and Acknowledgement

The app was previously maintained by **Xiaojing Zhu** (ADS, SSF), **Nick Ramirez** (ADS, SSF), and **Kimberly Fernandes** (ADS, Mississauga).

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