Nuts and Bolts of Monitoring Visits

Erin Ferraro, BSN, RN, OCN©, Nurse Educator
Elizabeth Ness, MS, BSN, RN, CRN-BC™, Director
Office of Education and Compliance

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1. *Overview of monitoring visits*
2. *Types of monitors*
3. *SOPs*
4. *SMV/IMV preparation*
5. *Management of essential documents*
6. *Responding to queries:*
   - *How to and timeline*

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Purpose

- To assure
  - rights and safety of patients (i.e., human subjects) are protected
  - reported trial data are accurate, complete, and verifiable from source documents
  - conduct of trial is in compliance with protocol, good clinical practice (GCP) and applicable regulatory requirements.

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Auditing

Monitoring

Monitoring + Auditing =
Solid Assurance of Quality

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When Do Monitoring Visits Occur?

- Frequency Depends on:
  - Complexity of the protocol
  - Disease being studied
  - Rate of recruitment
  - PI/staff experience
  - Site performance
  - Sponsor's SOPs
    - Frequency not dictated by FDA regs

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Monitors in the CCR

- Industry sponsor
- CCR-sponsor
  - Office of Sponsor and Regulatory Oversight (OSRO)
  - Sponsor and Regulatory Oversight Support Services (SROS) Contract
- CTEP/ETCTN: Theradex
- NCTN audits
- ASRC – CCR QM Program
  - Intervention studies
  - Observational studies

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Polling Questions

- Currently, do you have Industry sponsor monitoring visits?
- Currently, do you have OSRO/SROS monitoring visits?
- Currently, do you have Theradex monitoring visits?
- Currently, do you have ASRC visits?

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CCR SOPs

PM-12	NCI CTEP and Network Audits
PM-13	Industry-Sponsored Studies Monitoring and Audit Visits • CCR Supplemental Guidance for Use of NIH Box • Audit Record Request Form
PM-13a	Center for Cancer Research Sponsored Studies Monitoring and Audit Visits • CCR Supplemental Guidance for Use of NIH Secure Email File Transfer (SEFT) • Audit Record Request Form
PM-13b	Monitoring and Audit Visits by ASRC (Arctic Slope Regional Corporation)

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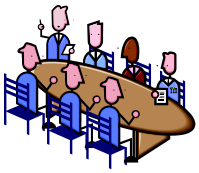
Who Attends a Monitoring Visit?



- Sponsor/CRO/CCR QM
  - Clinical Research Associate (CRA)/Monitor
- Site
  - PI, AIs
  - Clinical Research Coordinator
  - Data Manager
  - Pharmacist

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How is a Monitoring Visit Scheduled?

- Monitor contacts PI or CRC requesting the first monitoring visit (email)
  - Subsequent visits may be scheduled at the conclusion of a visit
- Date and time negotiated
- Monitor confirms via letter to PI
  - date and time
  - expectations of visit
  - which record/patients will be reviewed

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Notify CCR OEC of All Visits

- Notify OEC via the NCI CCR QA (nciccrqa@mail.nih.gov) mailbox:
  - Any scheduled monitoring visits, audits or inspections. Include the protocol number, PI, type of visit (e.g., routine monitoring, audit, FDA inspection), dates of the visit, name of the sponsor and which team member is the contact person for the visit.
  - All visit reports
  - Team response to monitoring and auditing visit reports

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Preparing for a successful monitoring visit

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Coordination of "Visits"…

- Clinical Center (CC) Regulatory Audit Guidelines
- Coordinate EMR access with HIMD *(*not needed for ASRC)*
  - Complete Regulatory Audit Scheduling Form
  - Send (via encrypted email) the list of medical records requested for access no later than the Wednesday prior to the week of the scheduled audit to CC-HIMD Regulatory Audits
- Routine monitoring/audit visits can be scheduled up to six months prior to the visit

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…Coordination of "Visits"

- Schedule a room, if in person visit
  - Schedule appt with pharmacy and/or research lab, if needed
- Provide information about access to the NIH campus to external monitor/auditor, if needed
- Prepare for visit

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Source Document Review…

- Assure medical records contain
  - All laboratory reports
  - X-ray, scan reports
  - Provider notes, nursing notes
  - Drug compliance/administration notes
  - Procedures documenting study parameters reported in CRF's
  - Informed consent ***process*** documentation
  - Informed consent documents for all participants, signed and dated
- Obtain missing information ***or*** document why unobtainable
- Upload to CRIS

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…Source Document Review

- Make sure laboratory reports and procedure reports are reviewed and signed by PI (if required per sponsor SOP)

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Review Pharmacy Records

- Pharmacy should review drug dispensing records prior to visit
  - Drug Accountability Record Forms (DARFs)
- Assure drug count is accurate
  - Disposal of returned meds
- Inform PI of discrepancies
- Assure “notes to file” are written for any discrepancies

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Review CRFs

- Assure CRF’s are complete, accurate, up to date
  - Data QC
  - Rave: study team review
- Review adverse events
  - Assure attribution of events is documented
- Review concomitant medications
  - Assure stop & start dates are recorded
- Review study medications
  - Assure stop & start dates are recorded
- Response Assessment

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Regulatory Review…

- Make sure Essential Documents (e.g., Regulatory File) are complete and up to date:
  - Protocol versions and approvals
  - Investigator Brochure versions/Package inserts
  - Lab certifications and normal ranges
  - Form 1572
  - CVs (signed and dated), licenses and Financial Disclosures for all Investigators
  - All IRB correspondence
  - All Sponsor correspondence
  - SAEs/Other reportable events
  - Delegation Log(s)
  - Screening/Enrollment Log

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How Do Essential Documents Get to the Monitor/Auditor?

OSRO/SROS

- PSO manager updates Veeva Vault

Industry Sponsor and CTEP

- CRC coordinates BOX access through OEC

ASRC

- Access via shared folders

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How Do Research Records Get to the Monitor/Auditor?

OSRO/SROS
- Send to monitor via SEFT

Industry Sponsor and CTEP
- Upload to BOX through OEC

ASRC
- Send to monitor via encrypted email

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Steps to Make the Visit Go Smoothly…

- Ensure monitor/auditor's current CV is in Medical Records
- Provide access to charts and files for participants and studies listed in letter only
- Confirm appointment times with PI and Pharmacy

- Arrange any paper documents in the designated room
- Greet monitor/auditor and escort to the designated room
- Escort monitor/auditor to pharmacy, research lab at appointed times

- Greet monitor/auditor over email, ensure they have access to source documents, regulatory file

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…Steps to Make the Visit Go Smoothly

- Review format of medical record with monitor/auditor
- Check in on monitor/auditor in short intervals to ensure all questions are answered
- Allow time to clarify information, e.g. corrections of CRFs
- For visits that are over multiple days, ensure that medical record and files are kept in a locked room
- Set up next visit at the end of the current visit

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Site's Expectations of the Monitor/Auditor

- Monitor/Auditor will come prepared
  - Be knowledgeable about the protocol
- Communicate honestly about findings
- Show cooperation, respect, and courtesy
- Appreciate the effort that went into the preparation

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Monitor/Auditor's Expectations of the Site

- Site will have prepared for the visit
- Records will be organized so they can work efficiently and finish on time
- Communicate honestly about findings
- Show cooperation, respect, and courtesy
- Appreciate the effort that went into the preparation

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After the Visit…

- Monitor/Auditor meets with PI/CRC to:
  - Share findings
    - May include events that require expedited reporting
  - Identify needed corrections, if applicable
  - Identify remedial training needs, if applicable
  - Answer questions
  - Set up next visit
- Monitor/Auditor will sign Visit Log, if not done already, and site staff will need to initial

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…After the Visit

- Site answers queries/clarifications
  - May be done during the visit
- Monitor/Auditor sends monitoring visit report
  - Placed in the Regulatory File
- Monitor/Auditor sends follow-up letter of thanks and confirmation of next visit

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General Process for Responding to Queries

- Work with DM, PI and/or PSO manager to address queries
  - Database
  - Written
- Review reports promptly as some findings (ie: major deviations, noncompliance) may require expedited reporting to the IRB
- Follow sponsor deadlines for addressing/ responding to queries
- Double check findings in regulatory binder, source documentation, database prior to addressing

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OSRO Policies and SOPs

Policies	SOPs
• 100 Quality Management System Policy • 101 Good Documentation Practices Policy • 203 Clinical Trial Records Policy • 205 Clinical Site Monitoring Policy	• 102-S01 Auditing SOP • 104-S02 Clinical Protocol Non-Adherence System SOP • 205-S01 Clinical Site Monitoring Plans – Development and Maintenance SOP

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OSRO/SROS Expectations of Site

- eCRF data entry and verification status is up to date
- Queries (in report and in database) addressed before the next IMV
- Missing essential documents uploaded before the next IMV

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SROS IMV Report: CRA resolution

NIH, NCI, CCR, OSRO Sponsor and Regulatory Oversight Support (SROS) Services

Interim Monitoring Visit Report (continued)

N. FOLLOW-UP / ACTION ITEMS

Status	Activity Type	Date Item Initiated	Description	Resolution	Completed Date
Open	eCRF Completion	15-Jun-2023	Subject 1010007: Per source documentation, height and body surface area were available but not recorded on the screening Physical Exam eCRF. Please verify and update the eCRF to include this data.		
Open	eCRF Completion	15-Jun-2023	Subject 1010007: Per source documentation dated 27-Mar-2023, the subject had history of prostate cancer, epidermolysis bullosa acquista, hypothyroidism, hyperlipidemia, Raynaud's phenomenon, and onychomycosis. This data was not recorded on the Past Medical History eCRF. Please update the eCRF per source documentation.		
Closed	Source Documentation	13-Apr-2023	Subject 1010003: The collection of CPC, Immune SEQ, and PBMC on 01/09/2023 and 4 BM aspiration were recorded on Research Sample Collection eCRF but source documentation to verify these data was not provided for review. Please provide source documentation for review.	The source documentation was provided for review.	15-Jun-2023
Closed	Source Documentation	13-Apr-2023	Subject 1010004: The source documentation to verify immune SEQ and BM biopsies at baseline or Day 1 was not provided for review. Please provide source documentation for review.	The source documentation for BM biopsies was provided for review. Deviation was filed for missed immune SEQ collection.	15-Jun-2023

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SROS IMV Report: CRA resolution

NIH, NCI, Center for Cancer Research (CCR)
Office of Sponsor and Regulatory Oversight (OSRO)
Sponsor and Regulatory Oversight Support (SROS) Services

FOLLOW-UP/ACTION ITEMS					
Status	**Activity Type**	**Date Item Initiated**	**Description**	**Resolution**	**Completed Date**
			Please provide.		
Done	Essential Documents	11-Oct-2023	The PI initials and date for the below site staff end date was missing on the Delegation of Authority (DOA) log: [redacted] Please update the DOA log.	The updated DOA log was provided for review.	03-Apr-2024
Done	Essential Documents	11-Oct-2023	The GCP and HSP training records were not provided for the following site staff listed on the Delegation of Authority (DOA) Log: [redacted] Please provide the training records.	The requested training records were provided for review.	03-Apr-2024
Done	Essential Documents	11-Oct-2023	The IRB Approval and the approved copy of the screening and standard informed consent version dated 01-Mar-2023 were not provided. Please provide.	The requested document was provided for review.	03-Apr-2024
Done	Essential Documents	26-Jan-2023	Please provide current GCP training records for the following site staff: [redacted] Staff Training Records will be reviewed again during the next IMV. If documentation of training is not available, a deviation report for which documentation is	The requested training record was provided for review.	03-Apr-2024

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SROS IMV Report: Site resolution

FOLLOW-UP/ACTION ITEMS					
Status	**Activity Type**	**Date Item Initiated**	**Description**	**Resolution**	**Completed Date**
			• Follow Up, PE FUP D90: Per CRIS, vitals occurred on 26-Dec-2023, however this data was not recorded in C3D. • Cycle 1, PKC1D1: Predose collection time for M7824 and M9241 was 10:16 in CRIS but 10:15 was recorded in C3D. Please verify and update the eCRF per the source document.	Vitals signs were added to C3D. PK collection time was updated in C3D.	4/18/24
Open	eCRF Completion	27-Mar-2024	Subject 1010019: Please review the queries for the following eCRFs and update as applicable: • Cycle 1, PKC1 D1: Per CRIS, M9241 post treatment collection time was 16:58, however 16:52 was recorded in C3D. • Ongoing, Procedures: Per CRIS, neck CT occurred on 11-Oct-2023, however this data was not recorded in C3D. • Ongoing, Adverse Events: Per CRIS, event colitis with onset date 18-Nov-2023 was recorded, however, per C3D it was recorded as diarrhea. Please reconcile. Please verify and update the eCRF per the source document.	PK collection time was updated in C3D. The CT Neck was added to the CRF. Colitis and diarrhea were both updated in C3D.	4/18/24 4/22/24
Open	Essential Documents	27-Mar-2024	The CAP Certificate for the Department of Laboratory Medicine expired on 11-Mar-2024. Please provide the updated CAP Certificate.	See attached CAP Certificate.	4/18/24
Open	Source Documentation	27-Mar-2024	Subject 1010019: Per CRIS, adverse event diarrhea, grade 2		

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What if I have a question about a SROS query?

- Call or email the monitor
- If you need more discussion to resolve a query, make a note for the next IMV.
  - OneNote
  - Add to your calendar for the visit
  - Add a note to the visit date calendar
  - Print report and highlight/make notes, use for discussion

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Query Response: ASRC

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ASRC IC/EC Audits

- **Frequency**: Monthly
- **Notification**: No pre notification; ASRC will email PI & CRC a report that will contain action items, if any
- **Turnaround time**: If any action items noted, responses due within two weeks
- **CRC role**: If no action items, save the report to the reg file/share drive. If action items – address in the word document and email back using "reply all" by deadline listed (two weeks)

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IC/EC Audit Findings

Review period: May 1-31, 2023	**Date reviewed:** June 23, 2023	
This log lists issues with Informed Consent and Eligibility for subjects enrolled on this study. This report is to confirm that all subjects enrolled were eligible and the Informed Consent process was conducted correctly.		
	Describe Event	**Site response**
Subject ID# 1010029 **On Study:** 05/25/2023	**Informed Consent** ▪ No issue found	
	Eligibility Review ▪ No issue found	

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IC/EC Audit Findings

	Describe Event	Site response
Subject ID# 1020002 **On Study:** 2/1/2023	**Informed Consent** 1. Documentation of Research consent was not available for review.	1. Noncompliance reported to the IRB on 4/5/2023.
	Eligibility Review • No issue found	

	Describe Event	Site response
Subject ID# 1020019 **On Study:** 2/3/2023	**Informed Consent** 1. Per documentation of research consent note dated 02/03/2023, subject signed consent version 10/5/2002. Per signed IC document, subject signed consent version 10/3/2022	1. CRIS documentation updated from 10/5/2022 to 10/3/2022 to reflect signed consent version.
	Eligibility Review • No issue found	

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IC/EC Audit Findings

Subject ID# RT00578 **On Study:** 10/31/2023	**Informed Consent** 1. Per signed Inform Consent, "X" consented the subject on 10/31/2023. Per PROTECT "X" is not authorized to consent subjects on this protocol.	12/5/2023, An RNI was filed with the IRB to inform them of the situation; PROTECT has been updated to reflect that "X is approved to consent. Acknowledgment letter from the IRB was received and no further actions need to be taken.
	Eligibility Review • No issue found	

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IC/EC Audit Findings

This log lists issues with Informed Consent and Eligibility for subjects enrolled on this study.
Please review and send your response within two weeks.

	Describe Event	Site response
Subject ID# 1010041 **On Study:** 9/18/2023	**Informed Consent** ▪ No issue found	
	Eligibility Review 1. Document supporting the following Inclusion Criteria was not available for review: ECOG performance of ≤ 2	
Subject ID# 1010042 **On Study:** 9/20/2023	**Informed Consent** ▪ No issue found	
	Eligibility Review 2. Document supporting the following Inclusion Criteria was not available for review: ECOG performance of ≤ 2	

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ASRC SMV Report Email Template

"Dear *PI*,

Please find attached a copy of SMV report for the Site Monitoring Visit conducted on *Dates*, *Year*, for the study *Protocol Number and Title.*

Please respond to the queries listed in the attachment **within four weeks of receiving the report.** The Word version of Issue Response Form is attached for your convenience.

Please do not hesitate to contact me if you have any questions or concerns."

- Note: Queries may include events that require expedited reporting to the IRB

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ASRC SMV Report: Site response

Subject ID	Describe Event	Site response
Subject # 1010005 **On Study:** 5/15/2022 **Off Study** N/A	**Laboratory Assessment** 1. Per protocol section 3.1.1, the following assessments will be performed at initial visit on 5/15/2022: Amylase, Lipase, LDH, total protein, GGT, uric acid, pro-brain Natriuretic peptide, T3 parathyroid hormone. Source documentation to verify the laboratory assessments were performed at initial visit was not available for review. Please verify and provide source document for review.	1. It appears that these labs were not ordered at the enrollment visit and deviation (deviation ID 13678) was filed.
Subject # 1010006 **On Study:** 7/05/2022 **Off Study** N/A	**Laboratory Assessment** 2. Per protocol section 3.1.1, the following assessments will be performed at initial visit on 7/05/2022: LDH, GGT, Parathyroid hormone, Anti-thyroid panel. Source documentation to verify the laboratory assessments were performed was at initial visit not available for review. Please verify and provide source document for review. 3. Per CRIS, Laboratory Assessments were performed on July 5-6, 2022, at initial visit. This data was not recorded on the CRFs. Please verify and update Laboratory CRFs per source document.	2. It appears that the LDH was not ordered and the other listed labs were cancelled. A deviation (deviation ID 13677) was filed. 3. As of Tuesday 05/30/2023, the July labs are recorded in the CRFs.
Subject # 1010026 **On Study:** 1/05/2023 **Off Study** N/A	**Initial Evaluation** 4. Per protocol section 3.1.1, ECOG performance status score will be performed at initial evaluation. Source documentation to verify the ECOG status was performed at initial evaluation on 1/05/2023 was not available for review. Please verify and provide source document for review.	4. Please refer to the Medical Oncology Progress Note on 01/12/2023 at 17:00 for the ECOG status.

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ASRC SMV Report: Site response

	Adverse Event CRF 4. Per adverse events log in CRIS dated 11/9/2020, grade 3 Pleural effusion that was started on 7/26/2020 and resolved on 8/16/2020 has an attribution of 3 in relation to disease. Per data recorded on the Adverse events CRF, grade 3 Pleural effusion has an attribution of 2 in relation to disease. Please verify and update the CRF per source document.	4. Attribution corrected on the AE CRF
Subject # 1010022 **On Study:** 1/12/2021 **Off Study:** 1/13/2021	**Screening** 5. Per CRIS Vital Sign Observation dated 01/12/2021, the subject had a heart rate (pulse) of 78 beats per minutes on 01/12/2021. Per data recorded on the Physical screening CRF, the subject had a heart rate (pulse) of 8 beats per minutes. Please verify and update the CRF per source document.	5. Heart rate corrected on the CRF.
Subject # 1010027 **On Study:** 9/19/2022 **Off Study:** N/A	**Prior Surgery Supplement CRF** 6. Per CRIS Inpatient operation note dated 09/16/2022, the subject had diagnostic laparoscopy performed on 09/16/2022. Per data recorded in the Prior Surgery Supplement CRF, the subject had diagnostic laparoscopy performed on 09/19/2022. Please verify and update the CRF per source document. 9. Per CRIS Inpatient operation note dated 09/16/2022, the subject had peritoneal washing and Esophagogastroduodenoscopy plus biopsies (EGD+Biopsy) performed on 09/16/2022. This data was not recorded on the Prior Surgery Supplement CRF. Please verify and update the CRF per source document. **On Study** 10. Per Protocol section 3.4.6, the Quality-of-Life questionnaires (QOL) will be completed at the pre-treatment evaluation prior to HIPEC (baseline), at 1 month, 3 months and then every 3 months (+/- 2 weeks) for 2 years. Per data available in CRIS, the subject had surgery with HIPEC on 10/11/2022, Post-Discharge Visits/Follow-Up month 1 on 11/11/2022 and Post-Discharge Visits/Follow-Up month 3 on 1/11/2023. Source documents to verify the QOL were completed at the above-mentioned timepoints were not available for review. Please verify and provide source document for review.	6. Date corrected on the CRF. 9. "Peritoneal Lavage, EGD" added. 10. Baseline survey dated 9/19/22 is in Labmatrix. A deviation has been entered for the other QOL timepoints that are missing.

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Resources

- SOPs
  - CCR
  - OSRO
- Orientation and resource manuals
  - General
  - CRC
- Orientation modules
- OEC

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Discussion Questions

- What have we missed?
- What works well for you that you can share?

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QUESTIONS?
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