ORACLE

ClearTrial 5.9 Release Supplemental Documentation

Support for Complex Trial Designs

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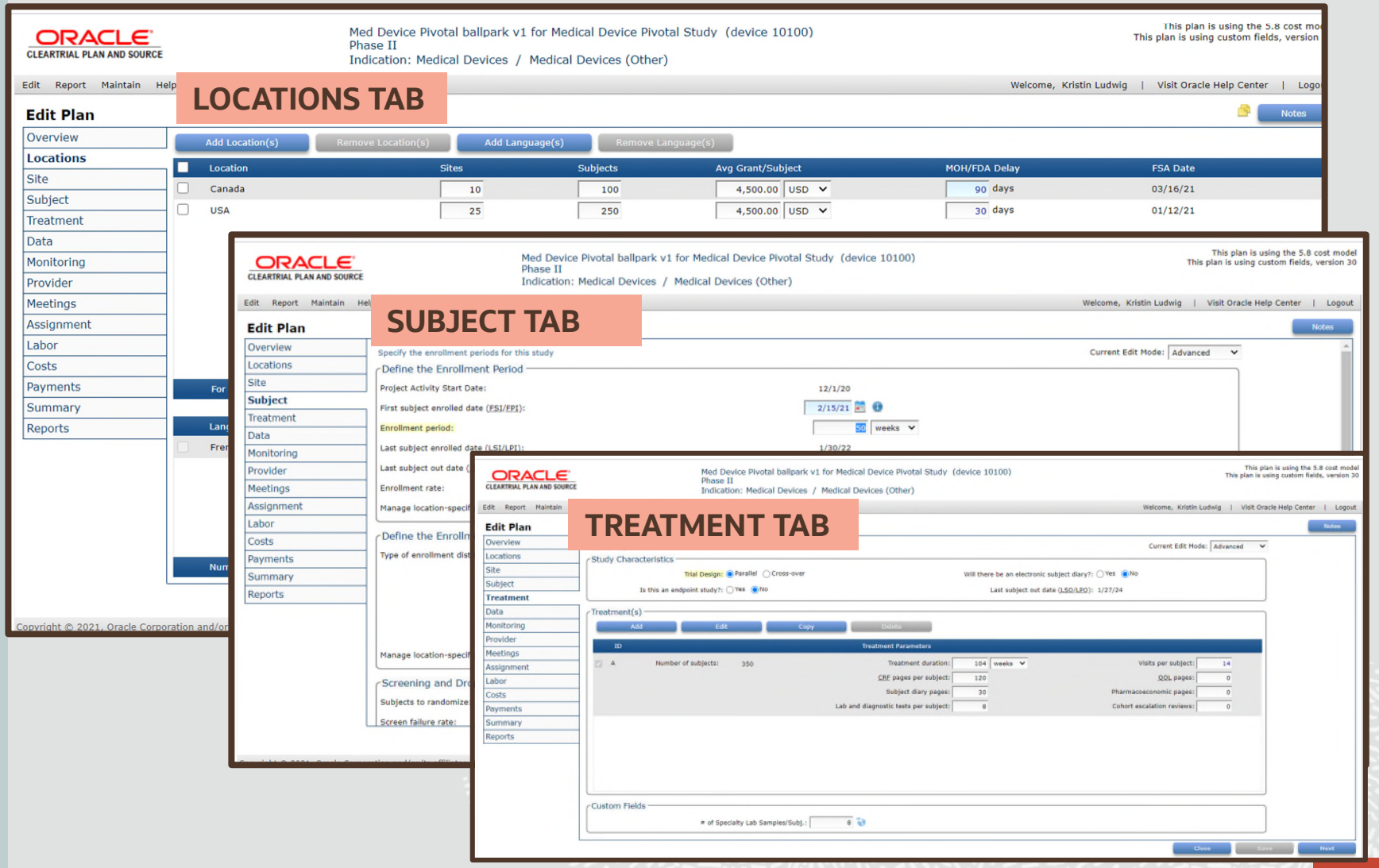
ClearTrial 5.9 Themes

- **Support multiple cohorts (26) with different enrollment characteristics**
- **Support long-term follow-up periods for non-terminating endpoints**
- **Consolidation of Investigator grant/payment-specific assumptions in one place**
- **New Milestone Dates (FSFV-LSLV)**
- **End of Study Planning Update**
- **Work Breakdown Structure (WBS) Updates**
  - Medical Monitoring
  - Project Management
  - Site Management
  - Data Management Task updates
  - End of Study (EOS) DB Lock, Stat Report, Final report
  - eTMF support
- **Increased usability for a more efficient user experience**

ClearTrial 5.9 UI Changes – Subject Assumptions < 5.8 Cost Model

OLD User Interface Design

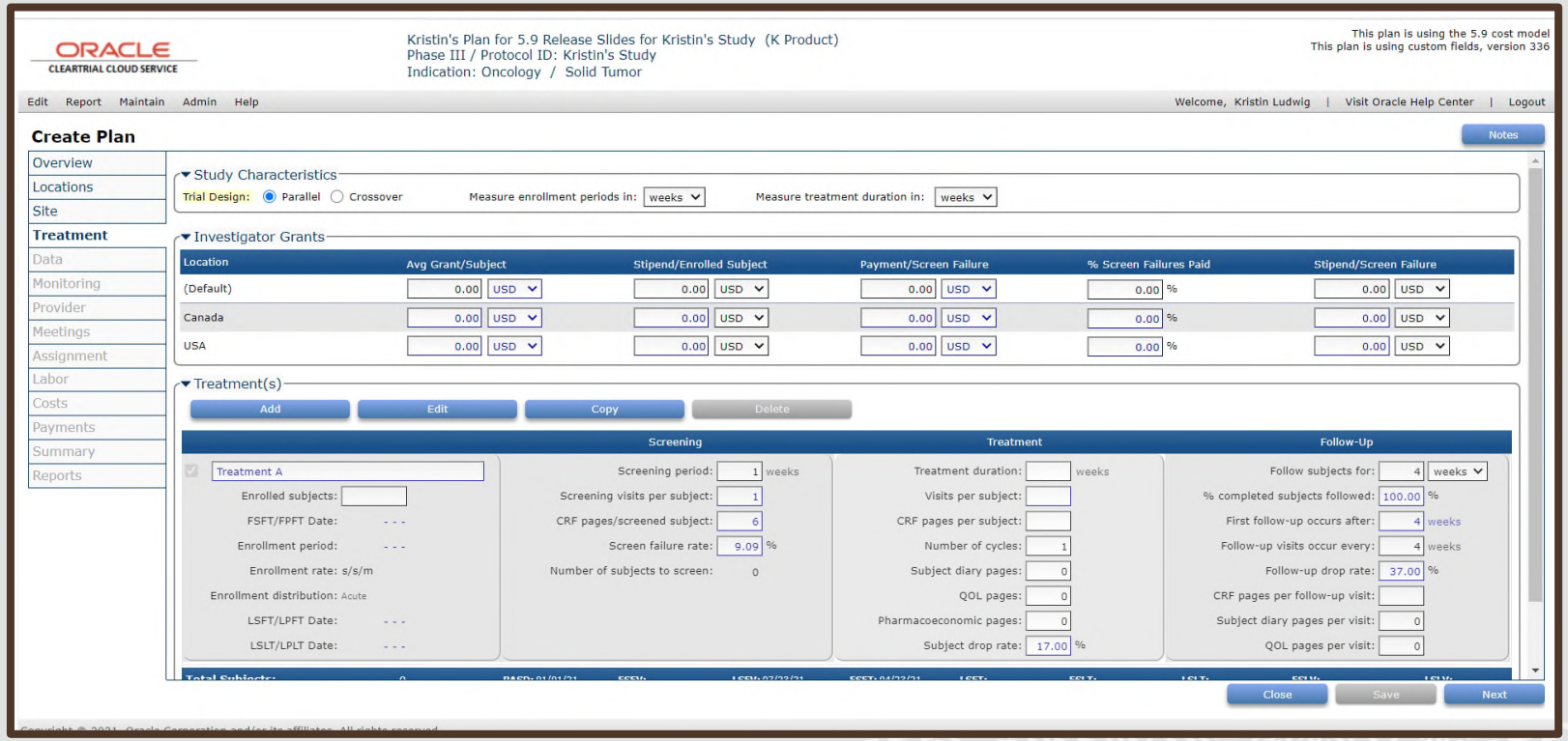
- **# of subjects** per location on the **LOCATIONS TAB**
- **Average grant per subject ($)** per location on the **LOCATIONS TAB**
- Only **one cohort** is supported per study plan, per location on the **SUBJECT TAB**
- **Enrollment Period, Enrollment Distribution,** are per study plan, per location on the **SUBJECT TAB**
- **Screening** and **Drops** are per study plan, per location on the **SUBJECT TAB**
- Model up to **5 Treatment Arms** on the **TREATMENT TAB**



5.9 User Interface Enhancements

NEW User Interface Design

- **Subjects** will be spread across locations by default according to the ratio of sites in that location to the total number of sites. Override the default spread by **editing each treatment/cohort** on the **TREATMENT TAB**
- All **Investigator grant/payment** related assumptions are entered in **one centralized location** on the **TREATMENT TAB**
- Model up to **26 staggered cohorts** on the **TREATMENT TAB**
- **Enrollment Period, Enrollment Distribution** are per location, per cohort on the **TREATMENT TAB**



5.9 Treatment Tab TRIAL DESIGN CONSIDERATIONS

- If all subjects will be on the same duration of treatment, with the same visit schedule you will only plan for 1 treatment group/cohort for all subjects.
- If subjects will have different enrollment characteristics, treatment durations, or different visit schedules, you will be able to plan these by creating multiple treatment groups/cohorts.

If you need more than one treatment group/cohort, you can click "Add" and define a different treatment group's parameters

Each treatment group/cohort is separated out into segments for general, screening, treatment and follow-up assumptions

Treatment(s)

Add | Edit | Copy | Delete

Screening	Treatment	Follow-Up

Dose A

Enrolled subjects: 79
FSFT/FPFT Date: 07/24/24
Enrollment period: 45 weeks

Screening period: 4 weeks
er subject: 1
ed subject: 6
ailure rate: 18.03 %

Treatment duration: 90 weeks
Visits per subject: 10
CRF pages per subject: 129
Number of cycles: 1
ject diary pages: 0
QOL pages: 0
Pharmacoeconomic pages: 0
Subject drop rate: 16.00 %

Follow subjects for: 4 weeks
% completed subjects followed: 100.00 %
First follow-up occurs after: 4 weeks
Follow-up visits occur every: 4 weeks

Dose B

Enrolled subjects: 79
FSFT/FPFT Date: 09/24/24
Enrollment period: 45 weeks

Screening p
Screening visits per su
CRF pages/screened su
Screen failur

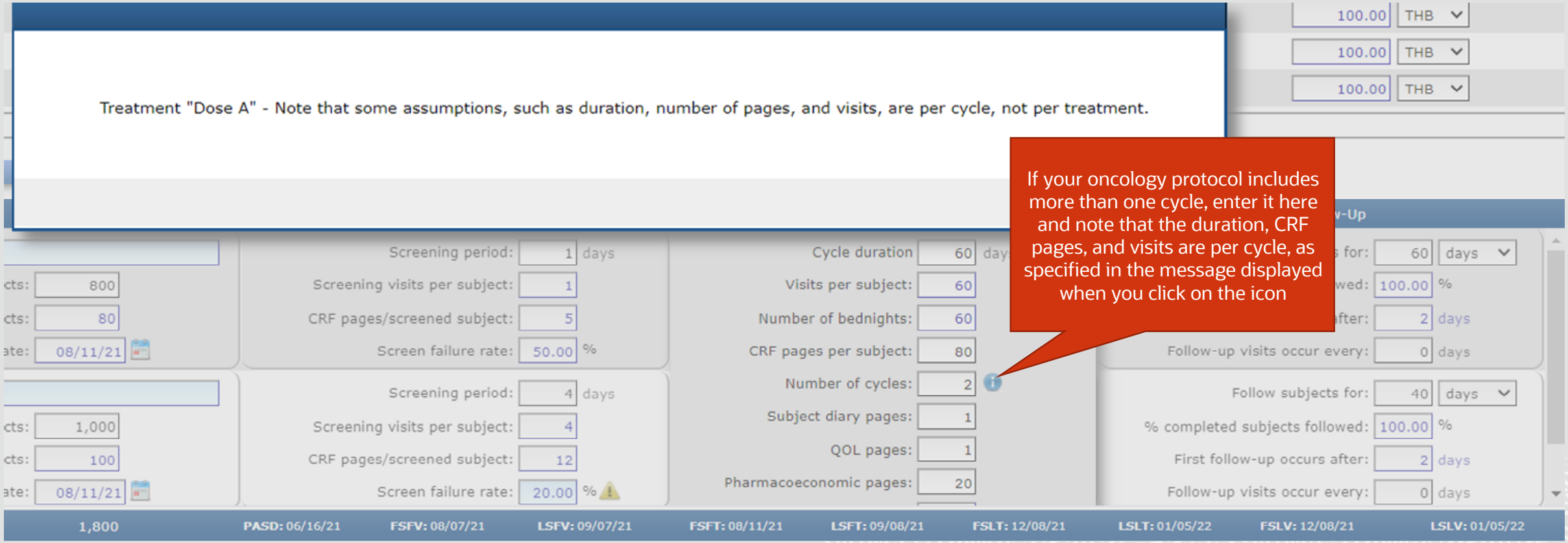
Follow subjects for: 4 weeks
% completed subjects followed: 100.00 %
First follow-up occurs after: 4 weeks
Follow-up visits occur every: 4 weeks

Total Subjects: 158 | PASD: 05/01/24 | FSFV: 06/26/ | T: 07/24/24 | LSFT: 08/04/25 | FSLT: 04/14/26 | LSLT: 04/25/27 | FSLV: 06/09/26 | LSLV: 06/20/27

Change the FSFT Date for those treatment groups/cohorts that start later than the first

When you have multiple treatment groups defined, click on any of the visible fields per segment to expand it to see ALL of the assumptions

5.9 Treatment Tab Updates – Number of Cycles for Oncology Trials



If your oncology protocol includes more than one cycle, enter it here and note that the duration, CRF pages, and visits are per cycle, as specified in the message displayed when you click on the icon

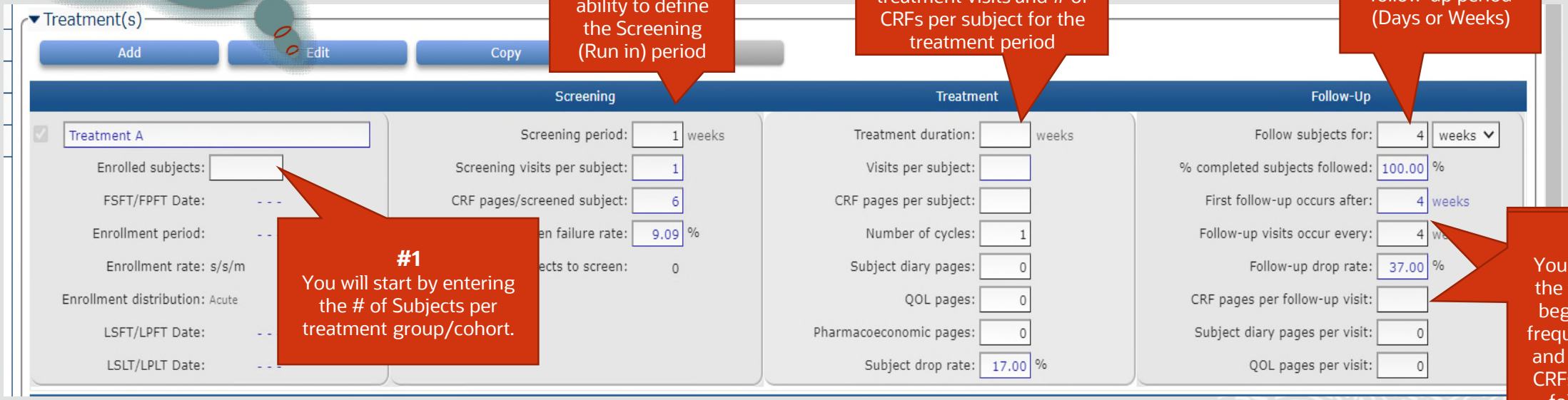
5.9 Treatment Tab Updates

TIP!
Click "Edit" to manage assumptions per treatment group/cohort, per location, and align the subject visit schedule to the Protocol's Schedule of Assessments

#2
You now have the ability to define the Screening (Run in) period

#3
You will then enter the treatment or cycle duration (wks/days), # of treatment visits and # of CRFs per subject for the treatment period

#4
You will then enter the duration of the follow-up period (Days or Weeks)



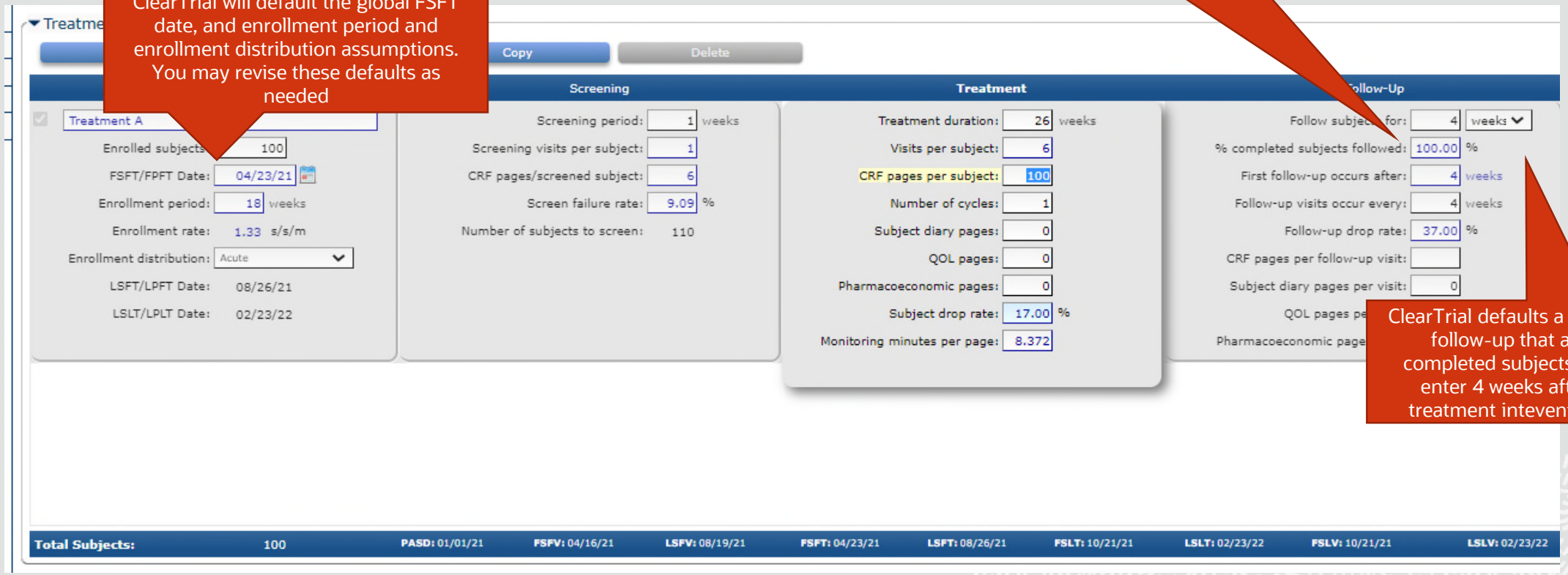
#1
You will start by entering the # of Subjects per treatment group/cohort.

#5
You will define when the follow-up period begins, the average frequency of the visits and the average # of CRFs/Subject for the follow-up period.

5.9 Treatment Tab Updates

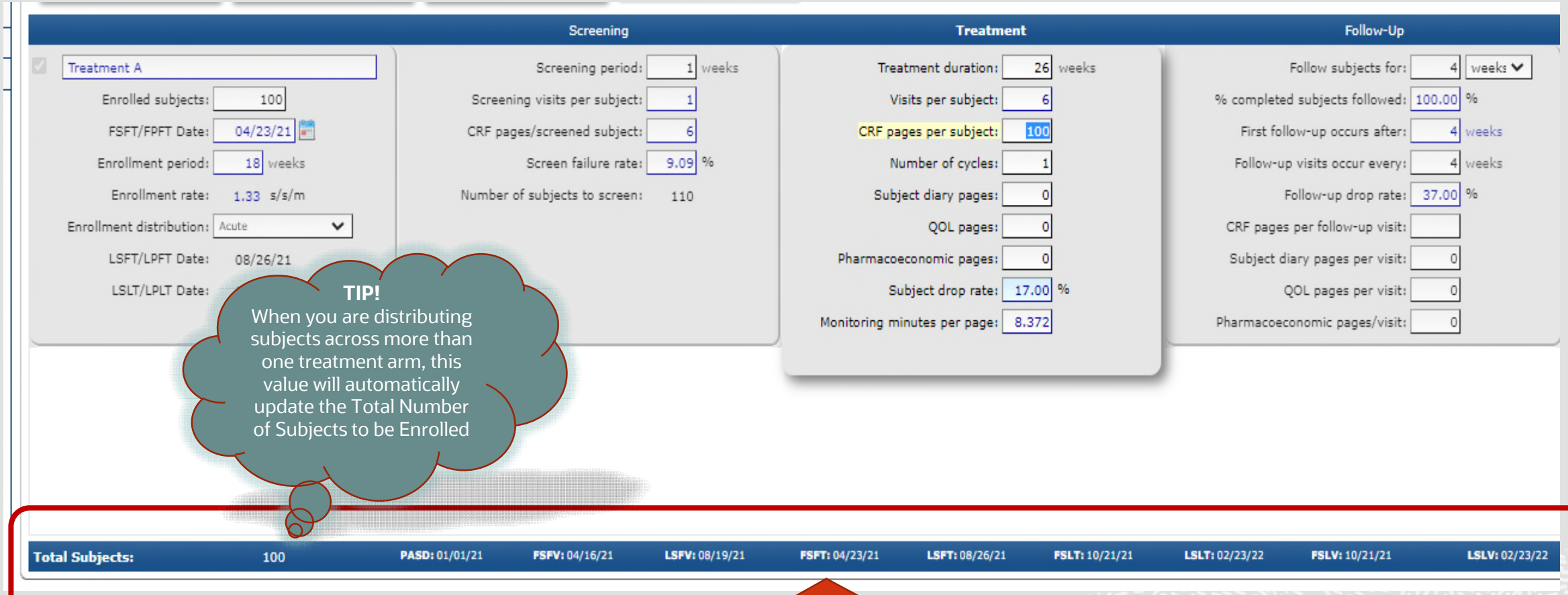
% completed subjects followed:
This value allows you to enter the % of subjects expected to complete treatment that will enter follow-up

Once you enter the #of Subjects, ClearTrial will default the global FSFT date, and enrollment period and enrollment distribution assumptions. You may revise these defaults as needed



ClearTrial defaults a safety follow-up that all completed subjects will enter 4 weeks after treatment intevention

5.9 Treatment Tab Updates – System Calculated Milestones



TIP!
When you are distributing subjects across more than one treatment arm, this value will automatically update the Total Number of Subjects to be Enrolled

You will see the total number of subjects allocated and global key milestone dates across all treatments/cohorts in the new summary bar

5.9 Treatment Tab Updates – System Calculated Milestones

PASD: 01/01/21	FSFV: 04/16/21	LSFV: 08/19/21	FSFT: 04/23/21	LSFT: 08/26/21	FSLT: 10/21/21	LSLT: 02/23/22	FSLV: 10/21/21	LSLV: 02/23/22

System Defined Milestone Dates – Definitions:

- **PASD:** Project Activity Start Date *(entered on the **OVERVIEW TAB**)*
- **FSFV:** First Subject First Visit *(First Subject Screening/Enrollment Visit)*
- **LSFV:** Last Subject First Visit *(Last Subject Screening/Enrollment Visit)*
- **FSFT:** First Subject First Treatment *(<5.8 Milestone: FSI)*
- **LSFT:** Last Subject First Treatment *(<5.8 Milestone: LSI)*
- **FSLT:** First Subject Last Treatment
- **LSLT:** Last Subject Last Treatment
- **FSLV:** First Subject Last Visit *(<5.8 Milestone: FSO)*
- **LSLV:** Last Subject Last Visit *(<5.8 Milestone: LSO)*

If the screening period is not defined or if there will be no data collected during screening, this visit will be the same as the First Subject First Treatment (FSFT) date

If the screening period is not defined or if there will be no data collected during screening, this visit will be the same as the Last Subject First Treatment (LSFT) date

If there is no follow-up expected this date will be the same as the FSLT date

If there is no follow-up expected this date will be the same as the LSLT date

5.9 Treatment Tab Updates

TIP!
By defining the first Treatment Group you can save time by copying the first treatment and only changing those values that are different between treatment groups

Treatment(s)

Add | Edit | Copy | Delete

	Screening	Treatment	Follow-Up
Treatment A			
Enrolled subjects: 100	Screening period: 1 weeks	Treatment duration: 26 weeks	Follow subjects for: 4 weeks
FSFT/FPFT Date: 04/23/21	Screening visits per subject: 1	Visits per subject: 6	% completed subjects followed: 100.00 %
Enrollment period: 18 weeks	CRF pages/screened subject: 6	CRF pages per subject: 100	First follow-up occurs after: 4 weeks
Enrollment rate: 1.33 s/s/m	Screen failure rate: 9.09 %	Number of cycles: 1	Follow-up visits occur every: 4 weeks
Enrollment distribution: Acute	Number of subjects to screen: 110	Subject diary pages: 0	Follow-up drop rate: 37.00 %
LSFT/LPFT Date: 08/26/21		QOL pages: 0	CRF pages per follow-up visit:
LSLT/LPLT Date: 02/23/22		Pharmacoeconomic pages: 0	Subject diary pages per visit: 0
		Subject drop rate: 17.00 %	QOL pages per visit: 0
Treatment B			
Enrolled subjects: 100	1 weeks	Treatment duration: 26 weeks	Follow subjects for: 4 weeks
FSFT/FPFT Date: 04/23/21	1	Visits per subject: 6	% completed subjects followed: 100.00 %
Enrollment period: 18 weeks	6	CRF pages per subject: 100	First follow-up occurs after: 4 weeks
Enrollment rate: 1.33 s/s/m	Screen failure rate: 9.09 %	Number of cycles: 1	Follow-up visits occur every: 4 weeks
Enrollment distribution: Acute	Number of subjects to screen: 110	Subject diary pages: 0	Follow-up drop rate: 37.00 %
LSFT/LPFT Date: 08/26/21		QOL pages: 0	CRF pages per follow-up visit:
		Pharmacoeconomic pages: 0	Subject diary pages per visit: 0

Total Subjects: 200 | **PASD:** 01/01/21 | **FSFV:** 04/16/21 | **LSFV:** 08/19/21 | **FSFT:** 04/23/21 | **LSFT:** 08/26/21 | **FSLT:** 10/21/21 | **LSLT:** 02/23/22 | **FSLV:** 10/21/21 | **LSLV:** 02/23/22

With a Parallel Study Design with two treatment groups on two different durations of treatment or different treatment schedules – the FPI date will stay the same

5.9 Complex Trial Planning Support

Supports Planning of Complex Trial Types including

- Multiple Treatment Groups/Cohorts (up to 26 groups)
- Dose Escalation trials or Expansion trial designs
- Adaptive Trials (where subjects treatment/follow-up durations may change)
- Extension Trials (that require ability to define long term follow-up)
- Umbrella/Bucket Trials (where subjects may continue treatment from a prior study that require multiple treatment/follow-up schedules)

5.9 Complex Trial Planning Support

Supports Supplemental CSR for Studies with Long Term Follow-up Periods

- DATA TAB: We now support the ability to have an initial DB lock and submission based on all the Subject Treatment data collected and including a Supplemental CSR for all the Subject Follow-up data collected.
- DEFAULT by Design: ClearTrial includes a standard 30-day safety follow-up after LSLT, so supplemental regulatory submissions are included by default. If these are not required for your particular trial design – see instructions below.

5.9 Complex Trial Planning Support

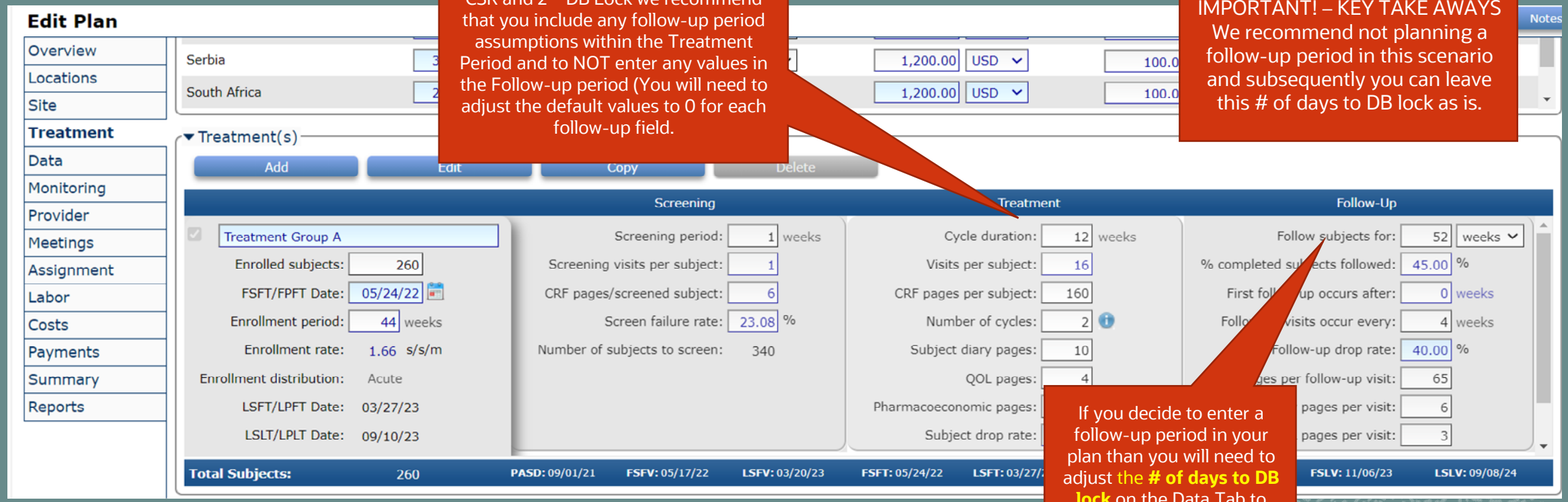
If NO supplemental CSR is planned (Guidance)

- If no supplemental CSR is planned for your study, you will need to modify the default assumptions of your template or plan to reflect “No” supplemental CSR on the Data tab.
- If a follow-up period is planned, but only 1 database lock for all subject data collected during treatment and follow-up, than you must adjust the # of days until DB lock to reflect the appropriate time from LSLV (Last Subject Last Visit) to DB Lock (+35 days)
- OR
- You can decide to include your follow-up period in your treatment period and indicate no follow-up period on the Treatment tab, and then you will not need to adjust the # of days until DB lock on the Data Tab.

5.9 Treatment Tab – Guidance If No Supplemental CSR is needed

If you do **not** require a supplemental CSR and 2nd DB Lock we recommend that you include any follow-up period assumptions within the Treatment Period and to NOT enter any values in the Follow-up period (You will need to adjust the default values to 0 for each follow-up field.

IMPORTANT! – KEY TAKE AWAYS
We recommend not planning a follow-up period in this scenario and subsequently you can leave this # of days to DB lock as is.



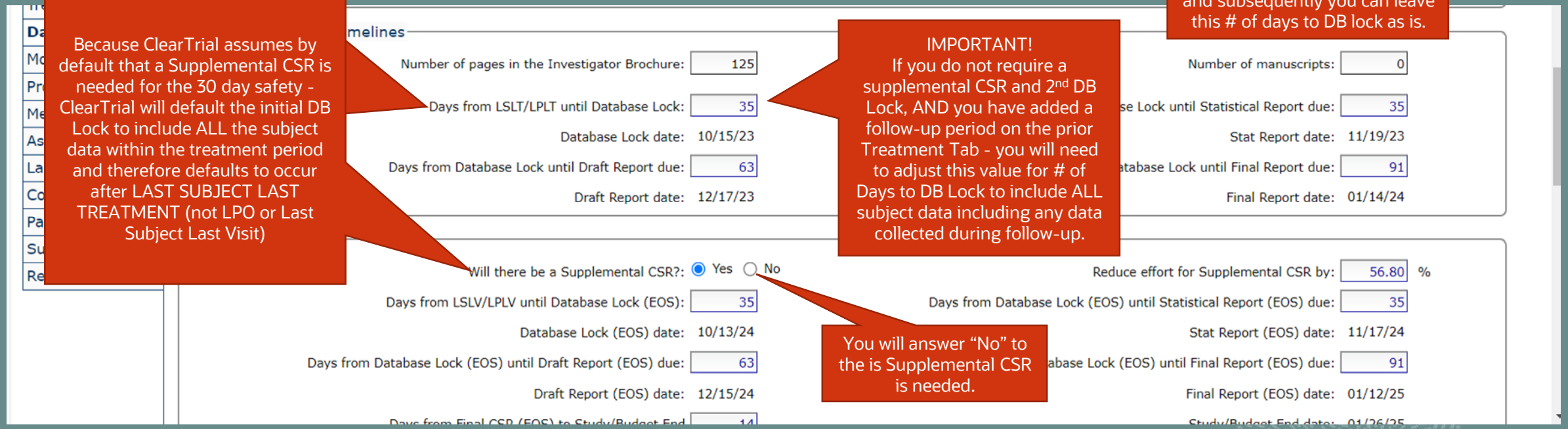
If you decide to enter a follow-up period in your plan than you will need to adjust the **# of days to DB lock** on the Data Tab to include this duration + the days from LSLV to DB Lock (+35 days)

5.9 Data Tab – If no Supplemental CSR is needed

IMPORTANT! – KEY TAKE AWAYS
We recommend not planning a follow-up period in this scenario and subsequently you can leave this # of days to DB lock as is.

Because ClearTrial assumes by default that a Supplemental CSR is needed for the 30 day safety - ClearTrial will default the initial DB Lock to include ALL the subject data within the treatment period and therefore defaults to occur after LAST SUBJECT LAST TREATMENT (not LPO or Last Subject Last Visit)

IMPORTANT!
If you do not require a supplemental CSR and 2nd DB Lock, AND you have added a follow-up period on the prior Treatment Tab - you will need to adjust this value for # of Days to DB Lock to include ALL subject data including any data collected during follow-up.



You will answer "No" to the is Supplemental CSR is needed.

Long-Term Follow-up Considerations

ClearTrial now includes the ability to adjust the Project Management default effort during long-term follow-up. The ClearTrial default is 75% reduction in oversight. Override this value in your Plan if you do not need any reduction in PM oversight to 0%

Reduce Project Management effort during Follow-up by:	75.00	%
Number of newsletters:	0	
Number of years to archive data:	10	

Multiple Treatment Groups/Cohorts (up to 26)

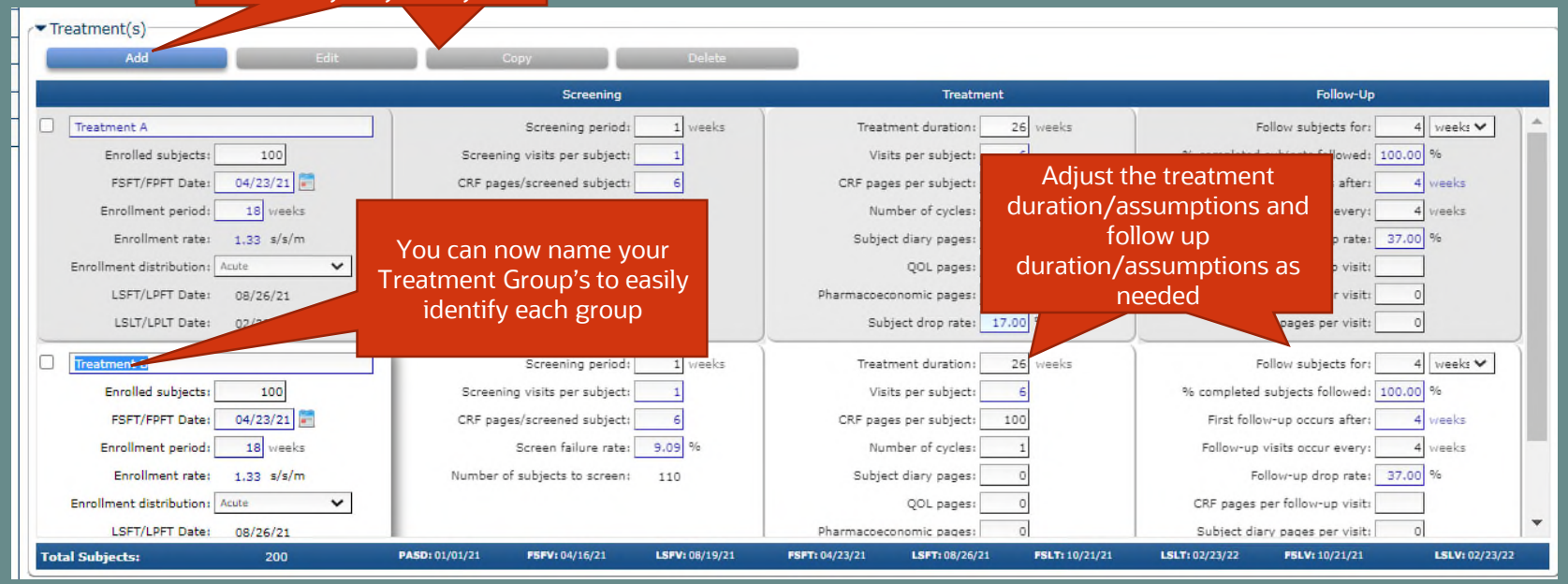
Multiple Treatment Groups/Cohorts

Key Considerations

- ClearTrial supports modeling up to 26 treatment groups/cohorts to plan complex trials such as Comparator studies, Oncology/Immuno-oncology studies, Survival studies, …etc.
- These multiple treatment arms can also represent Protocol Amendments and/or Extension arms (if not all subjects will continue treatment)

1. Select the initial treatment group and click "Copy" depending on the # of changes needed. You can also "Add" additional treatment groups, as needed.
2. Modify "Enrolled subjects" in treatment group A and group B.
3. Change the Name of the treatment group to easily identify or distinguish between varying treatments/cohorts.
4. Enter the treatment/cycle duration, depending on if there is 1 or more cycles.
5. Enter the CRFs and Visits per subject for the new treatment group.
6. Define the Follow-up period for the treatment group (if it differs)

Copy Treatment Group A if the treatment assumptions are similar – or Add a new treatment group (up to 26) if they vary widely



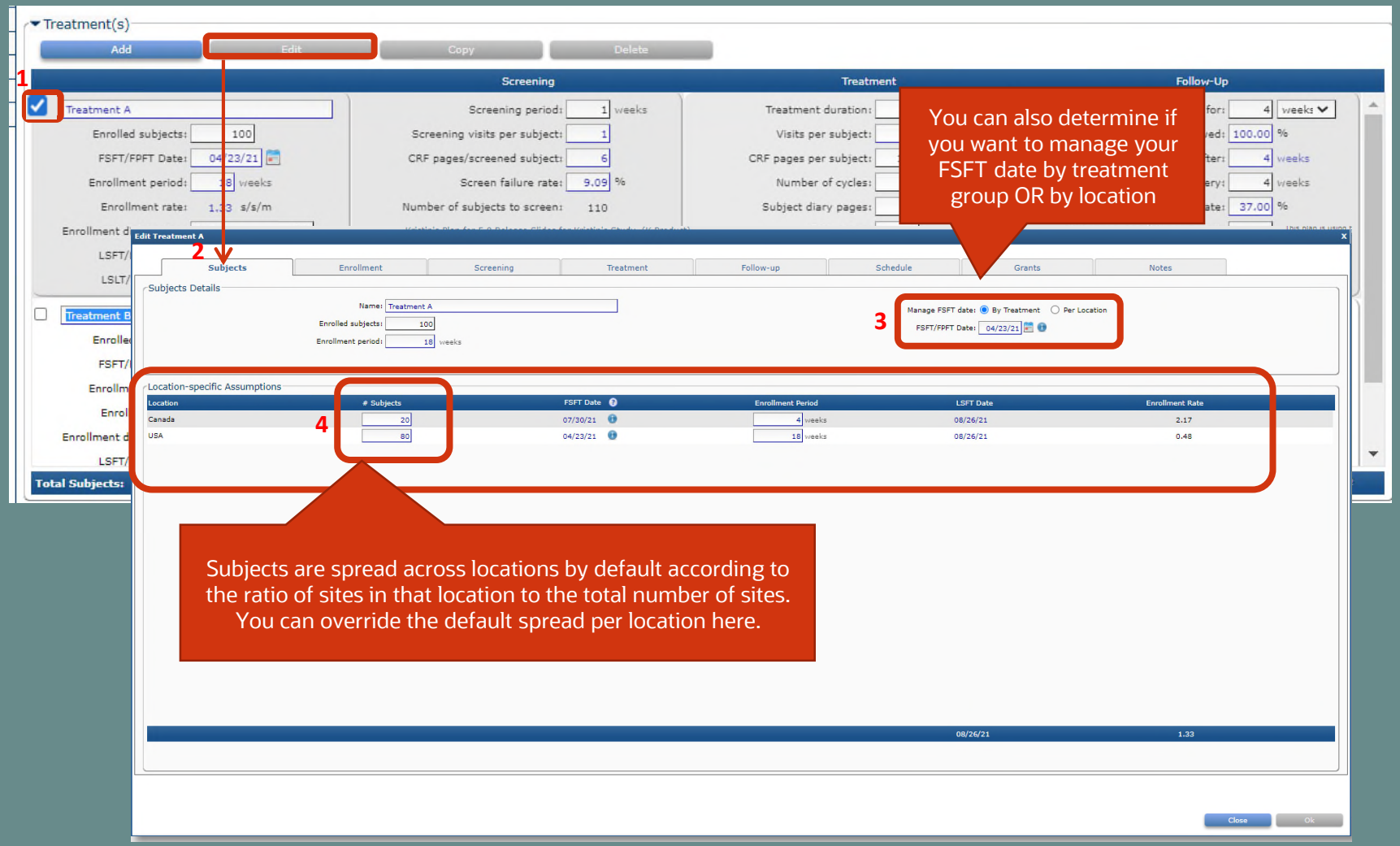
Multiple Treatment Groups/Cohorts

Key Considerations

- ClearTrial provides the ability to manage each Treatment Group/Cohort globally or by location.

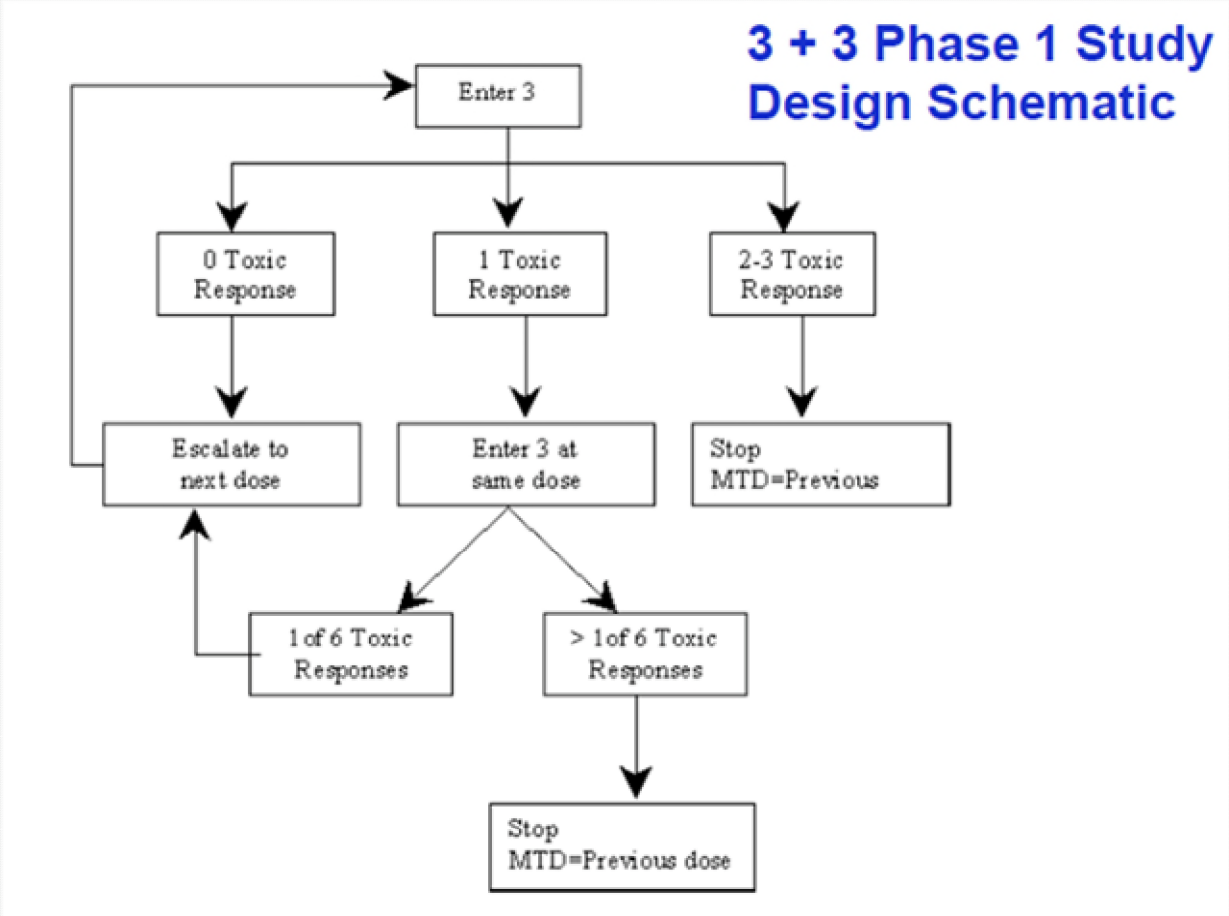
Clicks - Do This

1. Select the Treatment Group and then click "Edit"
2. You will be on the SUBJECT Tab
3. Choose to manage the First Subject First Treatment date for this treatment group by Treatment or by Location
4. You can override the default spread of enrolled subjects per location for this treatment group.



Dosing Escalation and Sequential Treatment Arms

MTD Trial Design



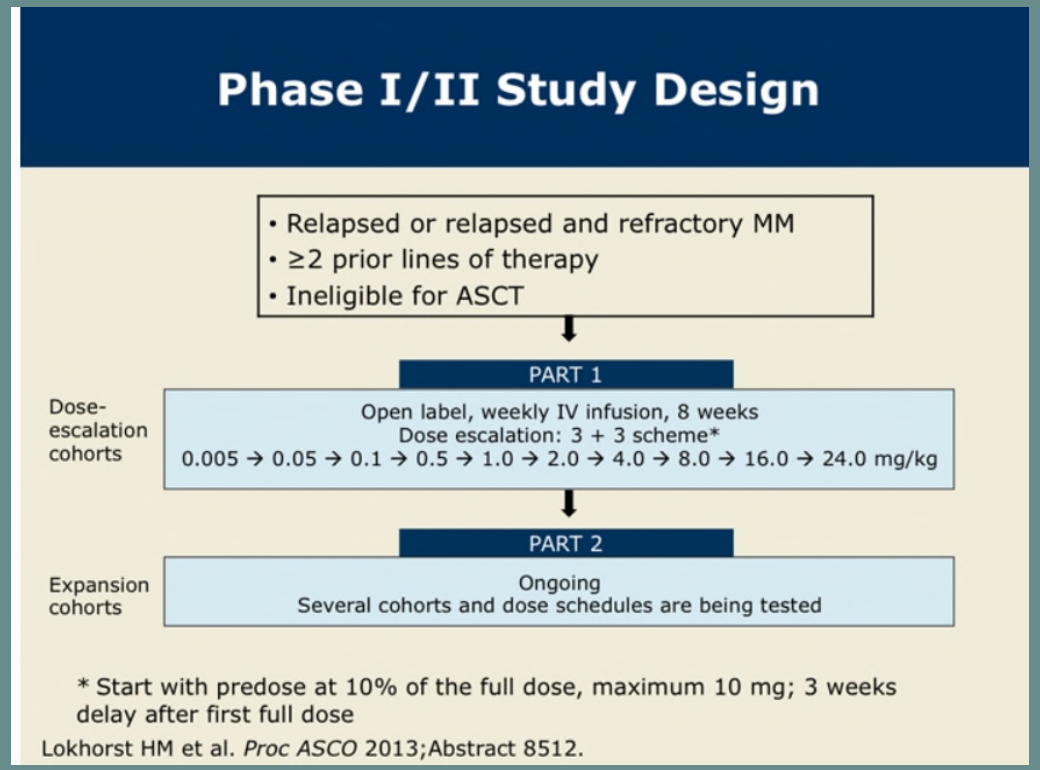
MTD (Tolerability)
Assume no Toxicity

Group 1= 3 Subjects
Enrollment period is 2 weeks
Treatment period is 2 weeks
No Follow-up Period
May need to adjust drop rate

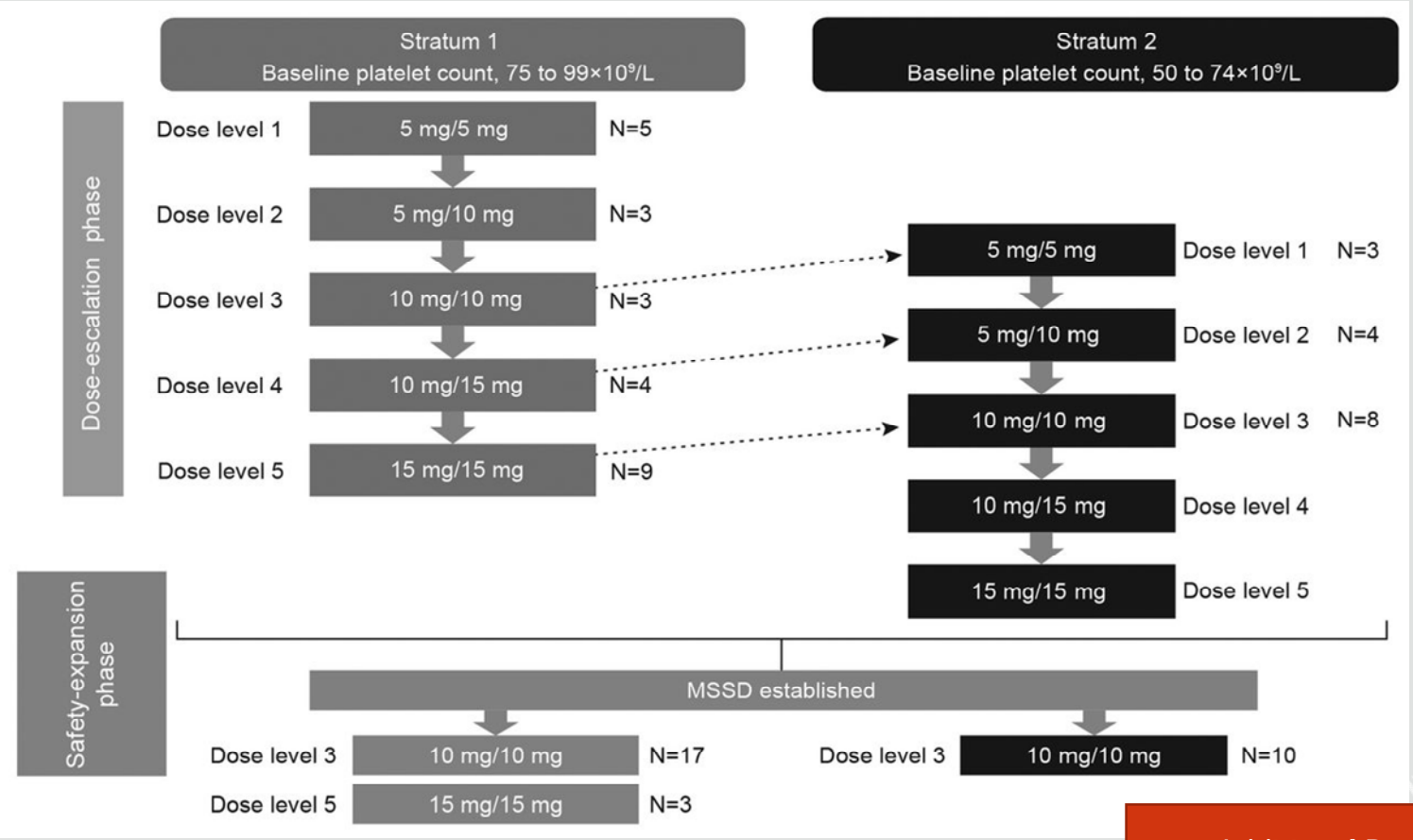
Pause to evaluate Patients (2 weeks)

Group 1= 3 Subjects
FPI Date is 2 weeks after
LSLT of Group 1
Enrollment period is 2 weeks
Treatment period is 2 weeks
No Follow-up Period
May need to adjust drop rate

Dose Escalation and Maximum Tolerable Dose (MTD) Trial Design



Dose Escalation and Maximum Tolerable Dose (MTD) Trial Design



3+ treatment arms

Stratum 1 = 24 Subjects
Enrollment period is 12 weeks
Treatment period is 8 weeks
No Follow-up period

Pause to evaluate Patients (3 weeks)

Stratum 2 = 24 Subjects
FPI Date is 3 weeks after LSLT of Stratum 1
Enrollment period is 12 weeks
Treatment period is 8 weeks
No Follow up period

Pause to evaluate Patients (3 weeks)

Stratum 3 = 48 Subjects
FPI date is 3 weeks after LSLT of Stratum 2
Enrollment period is 24
Treatment period is 4 weeks
Long Term Follow-up period is 12 weeks

Additional Dose Expansion Cohorts may be added

Adaptive Trial Design Considerations

Does the protocol provide assumptions for Adaptive Trials Design assumptions?

- How many subjects per treatment arm?
- When Does Adaption Begin (defines FPI dates for Treatment Arms)
- Define duration of treatment and follow up details per arm.
- # of visits per treatment
  - Do Subjects enter long term follow-up?
  - What is the drop rate from the treatment period to the follow up period?
  - How frequency are the subject visits during the follow-up?
- Additional Considerations:
- Type of data collected per treatment arm (ePRO, Medibles, Wearables, Home Care Visits, other/lab?)

How to Plan Adaptive Trials in ClearTrial

Pro-actively Plan for the Adaptive Trial Design

- If the protocol provides enough detailed assumptions to properly estimate the "decision points" for how treatment may change across the group of subjects then plan using the **Multiple Treatment Arms** functionality on the Treatment Tab.
- Add the # of Treatment groups needed to properly estimate the total "in-life" portion of treatments. Note only 5 Treatment arms allowed in 5.8 but up to 26 arms allowed in our next release of 5.9. Flexible treatment scheduling is targeted to be released later this year.
- Allocate the total # of subjects per treatment arm and plan the "average" duration of treatment, average # of CRFS per treatment, average # of subject visits per treatment and other key assumptions (# of labs/treatment, subject diary pages/treatment, QOL pages/treatment)
  - Custom Fields allows you to add other essential elements such as:
  - # of images, # of ECGs, # of PK labs, # of specialty/biomarker labs, and other ancillary vendor costs drivers. These are then used in the Cost tab configurations to build out these ancillary vendor fees.
- Adjust the treatment schedule during study execution if needed.

How to Plan Adaptive Trials in ClearTrial

Reactively Plan for the Adaptive Trial Design (reforecast the plan)

- If the protocol does not provides enough detailed assumptions to properly estimate the “decision points” for how treatment may change across the group of subjects you can begin by planning the average treatment duration for ALL subjects in one (1) treatment group.
- Once the study is under way, you can adjust your plan (Copy Plan, and revise treatment) based on the revised treatment schedule (for all remaining patients, or for a subset of patients).
- Enter the # of subjects already enrolled in the initial treatment arm and adjust the schedule and assumptions based on “actuals”.
- Create one or more treatment groups for the remaining subjects based on the revised protocol treatment schedule.
- Adjust the treatment schedule during study execution if needed.

Extension or Open Label Trial Design Considerations

Is the extension portion of the study known up front prior to the initial study start?

- If yes – you can include the extension/open label portion of the study in the initial study budget and leverage the Long Term Follow-up capabilities as well as Supplemental CSR capabilities..
- Will All Sites participate in the extension study? If yes, adjust site start-up activities if needed. If no, this may indicate needing to create a 2nd Plan vs. including in this plan.
- Will All Subjects from the initial study continue into the extension study? If Yes, you can include them in the follow-up portion of the treatment arm and set the drop rate % to 0% dropped subjects. You will have an opportunity to set a drop rate % for the follow-up period separate from the treatment period if needed.
- If there are different treatment arms for the extension study you can create multiple treatment arms and label the treatment arms "Extension…." to easily define them. You will set the FPI date for the Extension study to begin after last subject finishes treatment (and follow-up) from the initial portion of the study.

Extension or Open Label Trial Design Considerations

Is the extension portion of the study known up front prior to the initial study start?

- If no – you can create a new “Plan” under the same “Study” for the extension portion of treatment, and select a pre-configured “Extension Study Template” that will scope the services automatically.
- Considerations:
  - Site Start-up is not required or reduced
  - Regulatory Support is reduced
  - DM Build/Setup is not required or reduced
  - Safety Build/Setup is not required or reduced
  - Biostats TLFs can be re-used (no unique TLFs)
  - Monitoring effort will adjust based on scope of data. Further adjustments can be made for complexity of data.

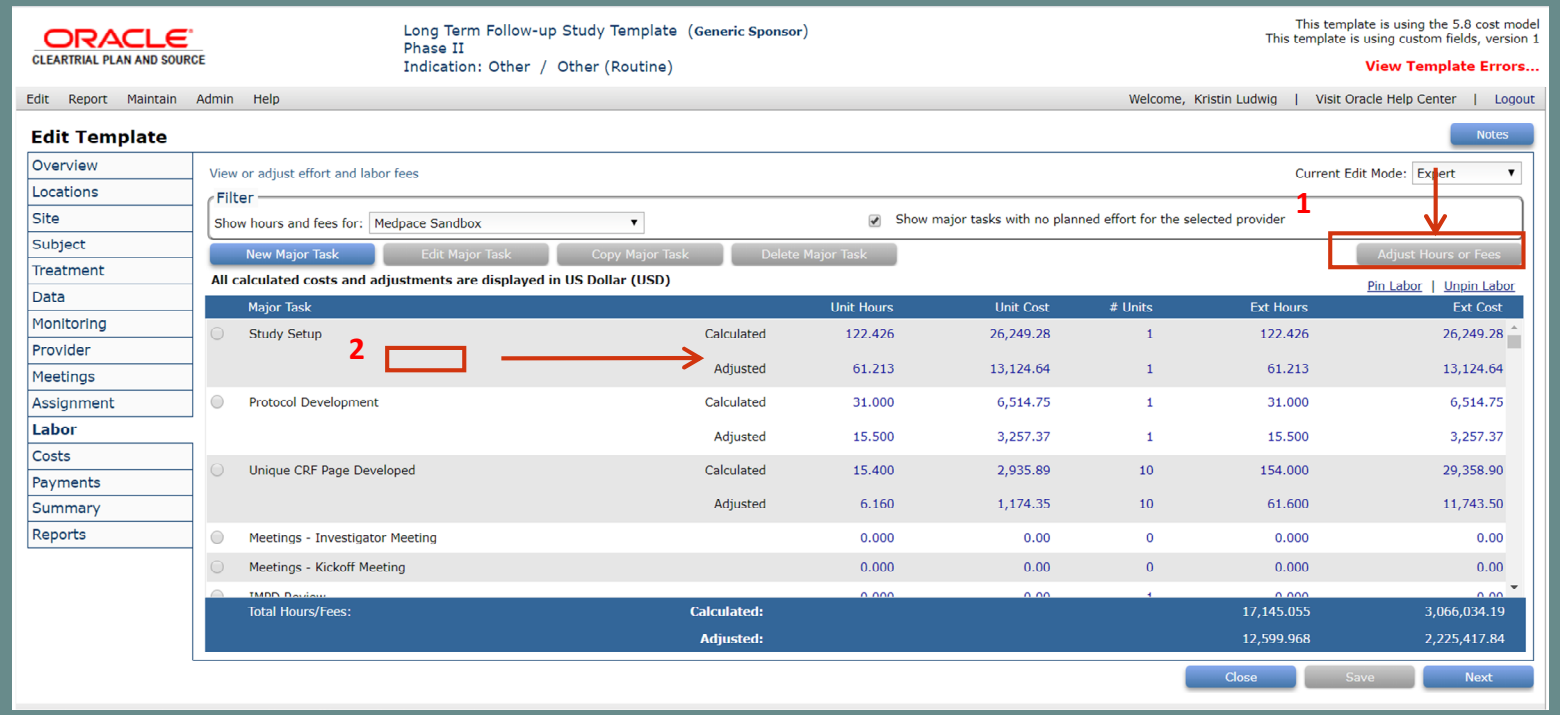
Extension Trial Planning

Talking Points

- Extension Study Templates can be created that pre-define the “efficiency factor %” for tasks that are are carried over from the initial study that do not require the full “build”

Clicks - Do This

1. From the Labor tab, you can select a Major Task and click on the “Adjust Hours or Fees” button in the top right corner to adjust the % of effort/fees to be reduced for “repeat work”
2. You can see how the Fees and hours are adjusted by viewing the Calculated amounts and the Adjusted Amounts in the User Interface.



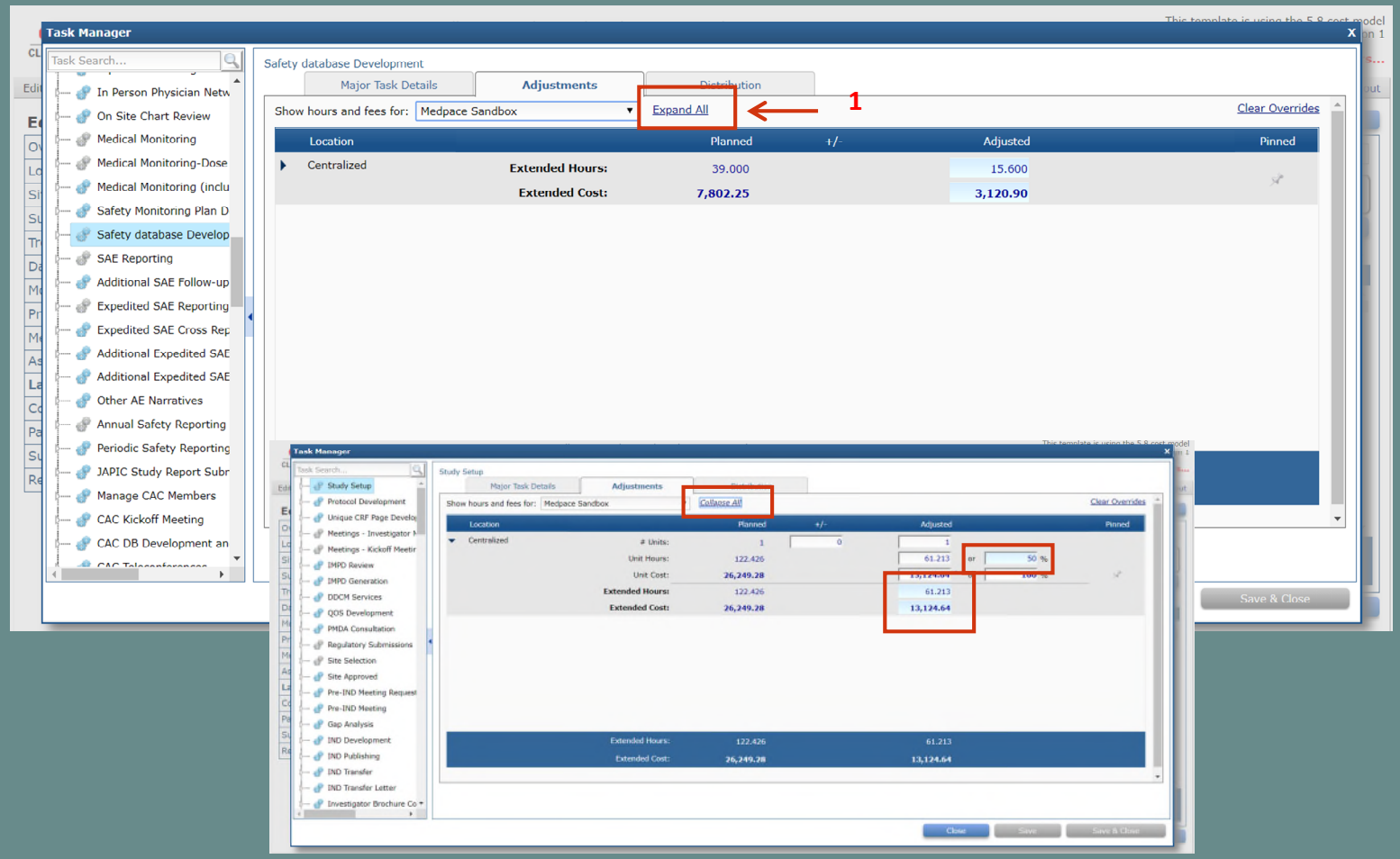
Extension Trial Planning

Talking Points

- Adjusting Hours and Fees (Top line adjustment)
- Can be done easily by clicking on the Major Task, and clicking "Adjust fees and Hours button")
- A new window will open to allow you to view, expand and adjust the Unitized assumptions as needed
- For example adjust hours by 50% will automatically adjust the hours and the fees.

Clicks - Do This

1. When the new window opens, you can view the roll up of the Hours and Fees, to make adjustments, click on the "Expand all" link and the fields will display for you to override the
    - Units
    - Hours or hour %
    - Fees or Fee %



Umbrella/Bucket Study Considerations

Will Subjects come into this Umbrella study that will continue on different durations of treatment?

- If yes – create multiple treatment groups for each treatment duration and adjust screening assumptions to 0%, and adjust follow-up period and drop rates as needed.
- If no – you can create a new “Plan” under the same “Study” for the extension portion of treatment, and select a pre-configured “Extension Study Template” that will scope the services automatically.
- Considerations:
  - Are the sites already activated and participating in the study?
  - Site Start-up is not required or reduced
  - Regulatory Support is reduced
  - DM Build/Setup is not required or reduced
  - Safety Build/Setup is not required or reduced
  - Biostats TLFs can be re-used (no unique TLFs)
  - Monitoring effort will adjust based on scope of data. Further adjustments can be made for complexity of data.

Questions?