DILIsym Services

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DILIsym User Training –

Using the DILIsym Monitoring Feature (i.e. Monitoring Clinical Biomarkers and Adaptive Design)

DILIsym Development Team

Goals for the Monitoring Training Session

Participants should understand the following general concepts:

- Applications of the Monitoring feature within DILIsym
- The critical components necessary for monitoring within DILIsym
- The behind-the-scenes structure of the DILIsym Monitoring feature
- The practical workflow for incorporating monitoring into a DILIsym simulation

Clinical Monitoring - General Introduction

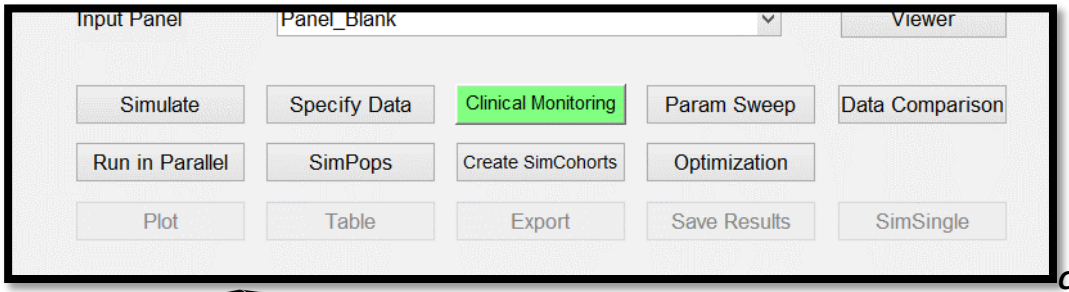
- Clinical monitoring is the practice of measuring outcomes during the course of clinical trials for the purpose of assessing certain endpoints and potentially altering course
- Some examples most relevant to DILIsym
  - Monitoring for elevations in liver safety biomarkers such as liver enzymes (ALT and AST), bilirubin, and others
  - Monitoring for levels of a drug or metabolite in circulation relative to a pre-defined safety risk threshold
- Typically, when monitoring is conducted during a clinical trial or post-marketing of a drug, certain criteria are defined for resulting actions
  - Elevations above certain levels could lead to cessation of treatment
  - Other actions could include follow-up protocols, dose escalation or de-escalation, or increased frequency of monitoring
  - FDA guidance documents on liver safety provide some information

Some Applications of DILIsym Monitoring

1. Monitor liver safety related outcomes and adjust clinical protocol in real-time during simulation
   - e.g., Hy's Law biochemical criteria, other biomarkers
2. Monitoring levels of drug or metabolite and adjust clinical protocol in real-time during simulation
3. Titrate dose levels up or down depending on monitored levels
4. Terminate simulations when specified condition is met

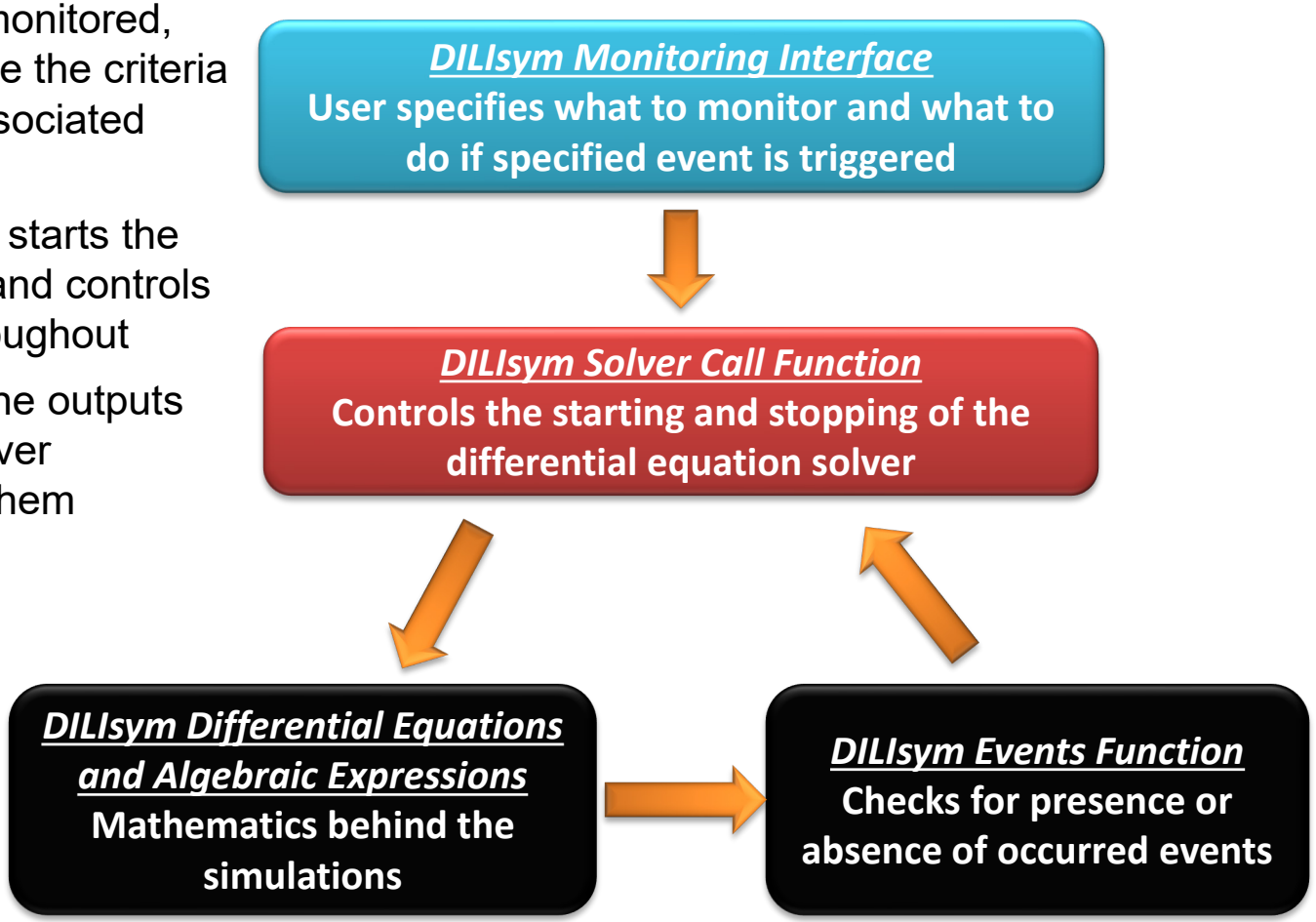
All DILIsym outcomes can be monitored

Only drug dosing parameters can be changed based on monitoring events in DILIsym v7A



The Behind-the-Scenes Structure of the DILIsym Monitoring Feature

- The monitoring interface allows the user to specify what is monitored, what action is taken once the criteria are met, and various associated timing aspects
- The Solver Call function starts the equation solver initially and controls the starts and stops throughout
- The equations provide the outputs from DILIsym as the solver progresses and solves them
- The Events function checks for the criteria defined by the user at intervals and over time windows specified by the user
  - *The longer the window for checking, the more the computational burden*



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DILIsym Monitoring Tool – Critical Components

1. SimSingle (simulation setup) within DILIsym via the home screen
   - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
   - A simulation needs to be set up, during which monitoring will occur
2. Specification of monitoring conditions using the DILIsym Monitoring interface for Condition Set 1
   - Goal is fully defined criteria for event to monitor for and resulting actions
   - Time associated aspects (frequency, time window, delay, etc.) are important to understand fully when defining conditions
3. Repeat Step 2 for Condition Sets 2-4, if applicable
   - Multiple scenarios for monitoring can be specified, up to 4 total, simultaneously
   - Condition Sets can be dependent (sequential) or independent (parallel)

DILIsym Monitoring Tool – Step By Step Instructions

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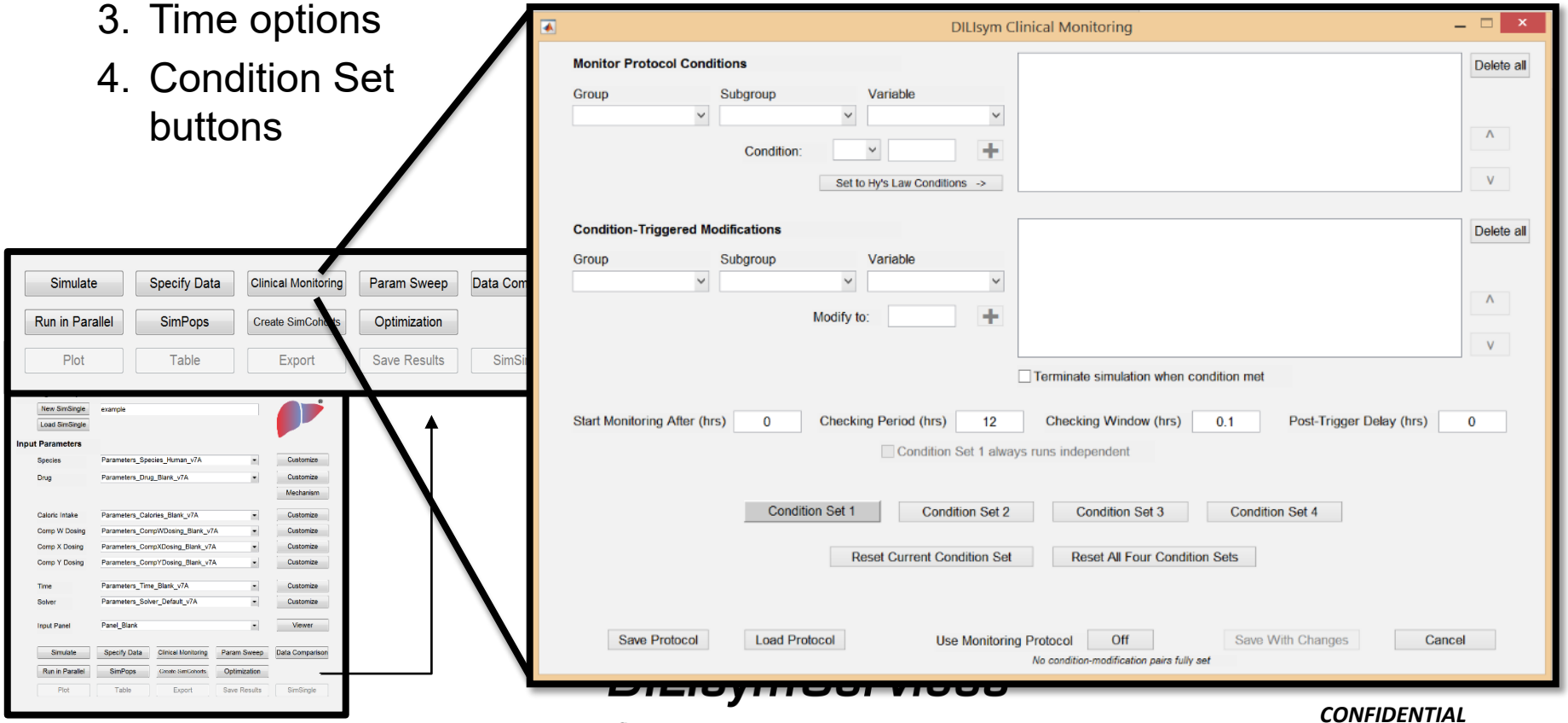
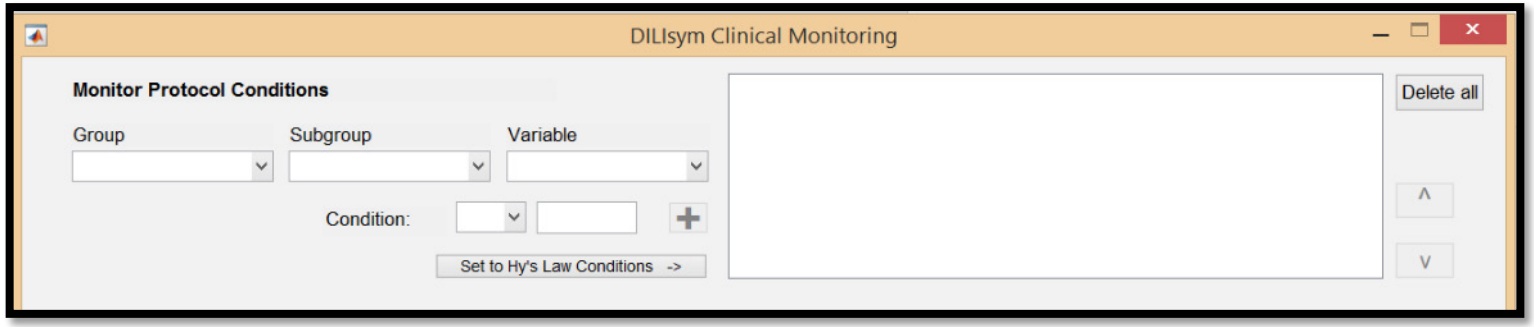
The DILIsym Monitoring Feature is Accessed from the DILIsym Home Screen

- The monitoring window has four main sections:
  1. Monitor Protocol Conditions
  2. Condition-Triggered Modifications
  3. Time options
  4. Condition Set buttons

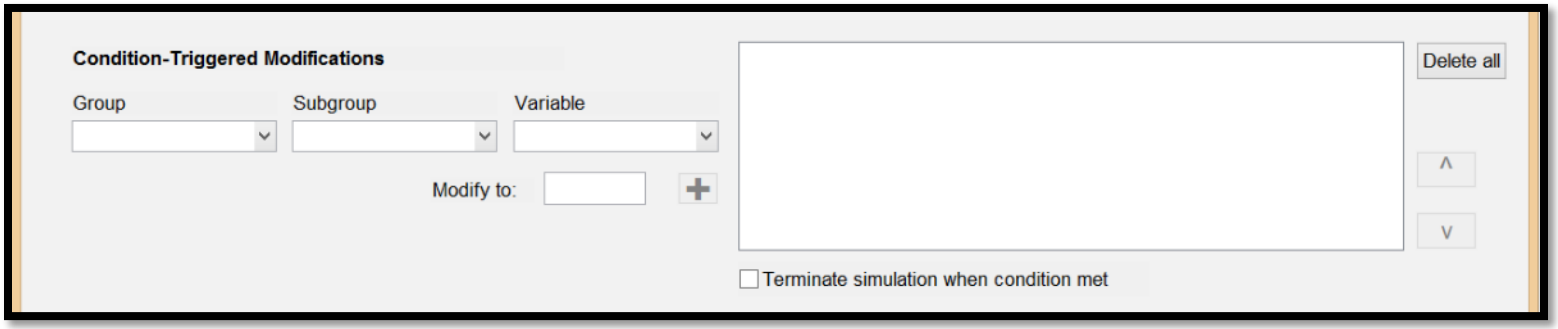


Add Your Intended Condition
Set 1 Monitoring Conditions



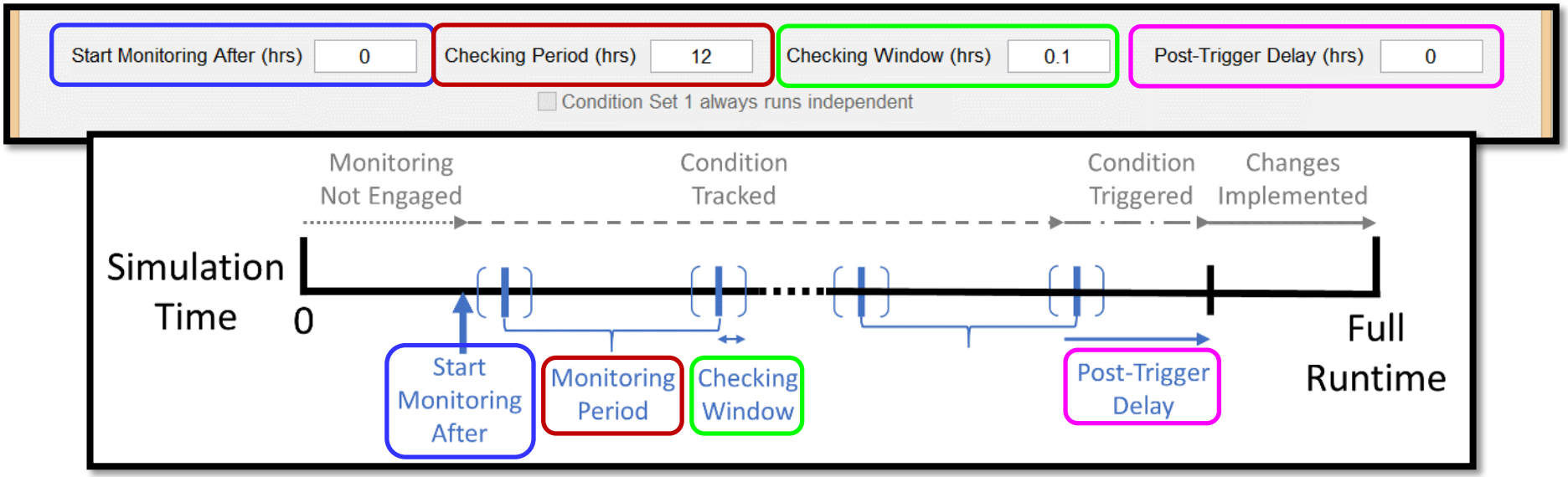
- The DILIsym output is selected from the drop-down menus marked “Group”, “Subgroup”, and “Variable”
- The condition is defined by **=**, **>**, or **<** the output monitored
- The “Set to Hy’s Law Conditions” button automatically populates the parameter table with the biochemical components of satisfying Hy’s Law
  - ALT > 3X ULN
  - Total bilirubin > 2X ULN
- Several outputs can be added to the table
- ***Each set of outputs within a given Condition Set must ALL be met for the Condition-Triggered Modification to take place (i.e., within a Condition Set, the criteria is AND across all outputs added to trigger the Condition-Triggered Modification)***

Add Your Condition-Triggered Modifications for Changes to the Simulation Upon Reaching the Monitored Condition(s)



- The DILIsym dosing parameter selected to change is selected from the drop-down menus marked “Group”, “Subgroup”, and “Variable”
- The new value is placed in the “Modify to:” box as a scalar and the parameter is added with the green “**+**” symbol
- Alternatively, users can select the “Terminate simulation when condition met” check box
  - This option stops the equation solver once the condition is met, after the delay between condition and action, if applicable
  - When the terminate option is invoked, there is no need to define a dosing change, as the simulation will not progress to enact the dosing change

Set the Options Related to the Timing of Monitoring



- ***Start Monitoring After*** – this option specifies a delay between the start of the simulation and the start of monitoring
- ***Checking Period*** – interval between monitoring, analogous to internal between lab testing days during clinical trial
- ***Checking Window*** – period of time during which the specified outputs are checked within the events function
  - The larger the checking window, the more computational burden incurred
  - If the window is too small, the solver could step over the monitoring time window
  - We recommend a minimum Checking Window of 0.1 hours, and an approximate maximum of 1-2 hours
- ***Post Trigger Delay*** – delay between when condition is met and when Condition-Triggered Modification occurs

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   - Multiple scenarios for monitoring can be specified, up to 4 total, simultaneously
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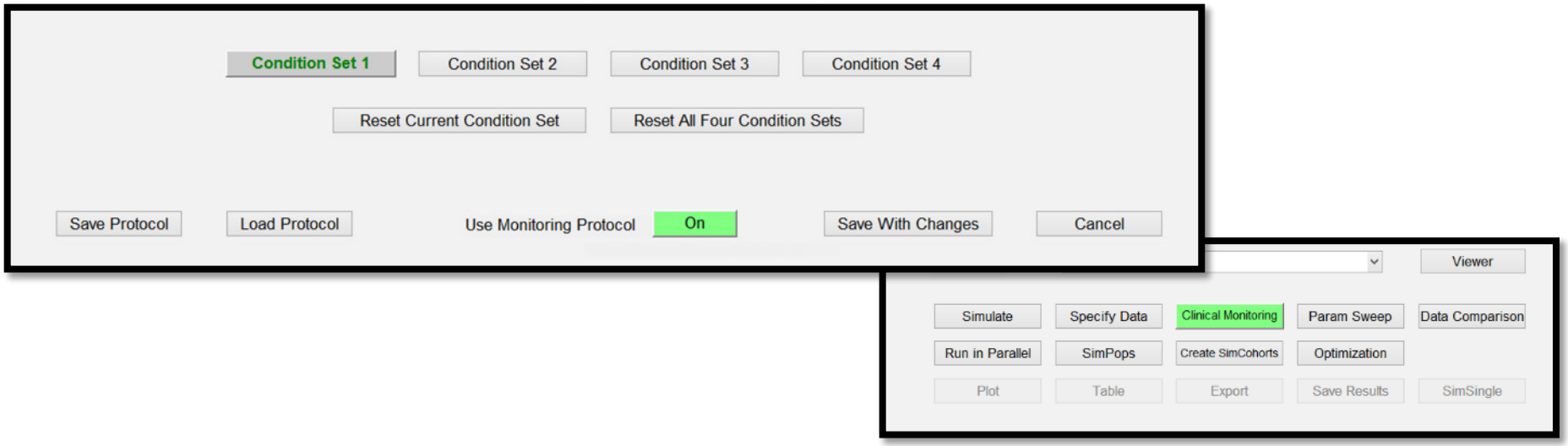
The Condition Set Buttons Allow Toggling Between Different Condition Sets

- 4 Condition Sets are available for use
  - Each set of outputs within a given Condition Set must ALL be met for the Condition-Triggered Modification to take place (i.e., within a Condition Set, the criteria is AND across all outputs added to trigger the Condition-Triggered Modification)
- Condition Sets can be dependent on prior Condition Sets (e.g. Condition Set 2 will not be monitored until Condition Set 1 is met) or they can be independent
- Once a given Condition Set is fully defined and capable of being used for monitoring, the button text will turn **green**
- When a monitoring setup is saved, all 4 Condition Sets are saved

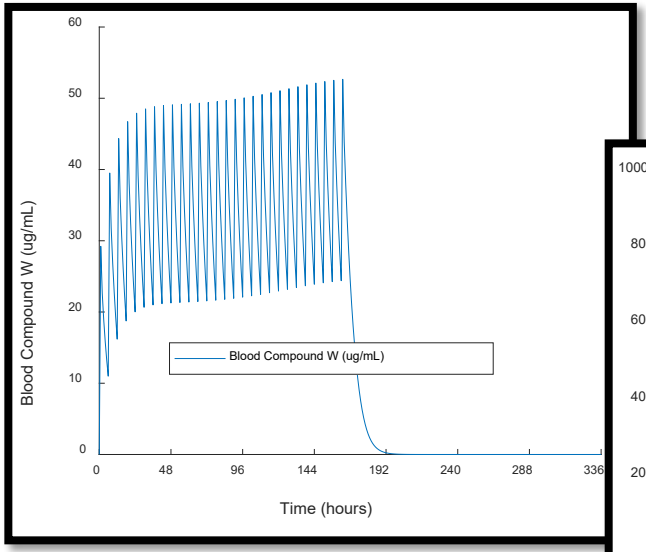
The “Use Monitoring Protocol” Button Should be Green and Marked “On” for Monitoring During the Simulation

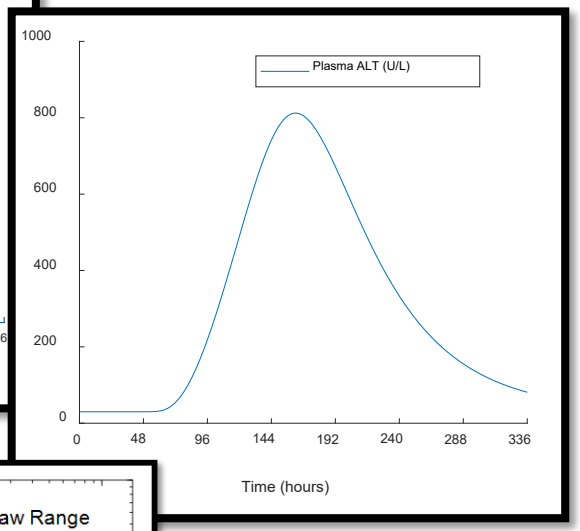


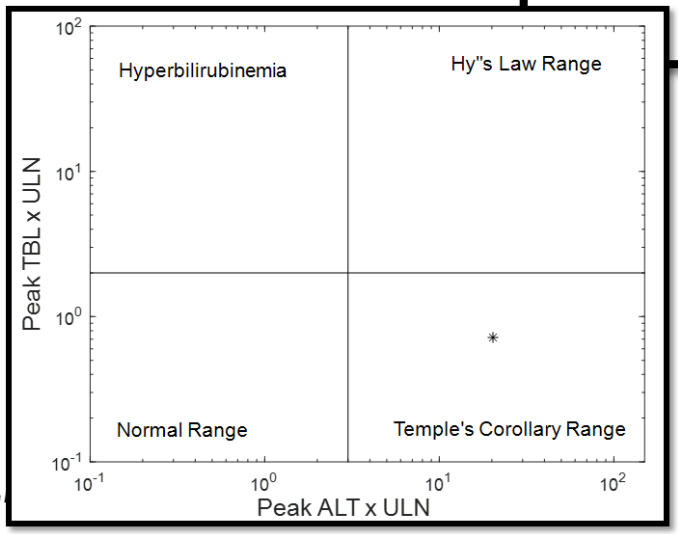
- Once the monitoring protocol is defined, push the “Use Monitoring Protocol” button
- “Save Protocol” and “Load Protocol” options are available for saving the setup and are recommended to facilitate re-use with other SimSingles
- The “Save with Changes” button must be pushed for closing the figure to enact the monitoring within the SimSingle
- Once the figure is closed, the DILIsym home screen “Clinical Monitoring” button will appear green within the SimSingle setup

Hands-on Monitoring Example – Cessation of Dosing at Specified ALT Value

- Goal is to monitor for ALT above 120 U/L and stop dosing
- APAP is dosed for one week
- Resulting PK, ALT, and eDISH plots shown at right without monitoring
- Example is simplified for the purposes of illustration



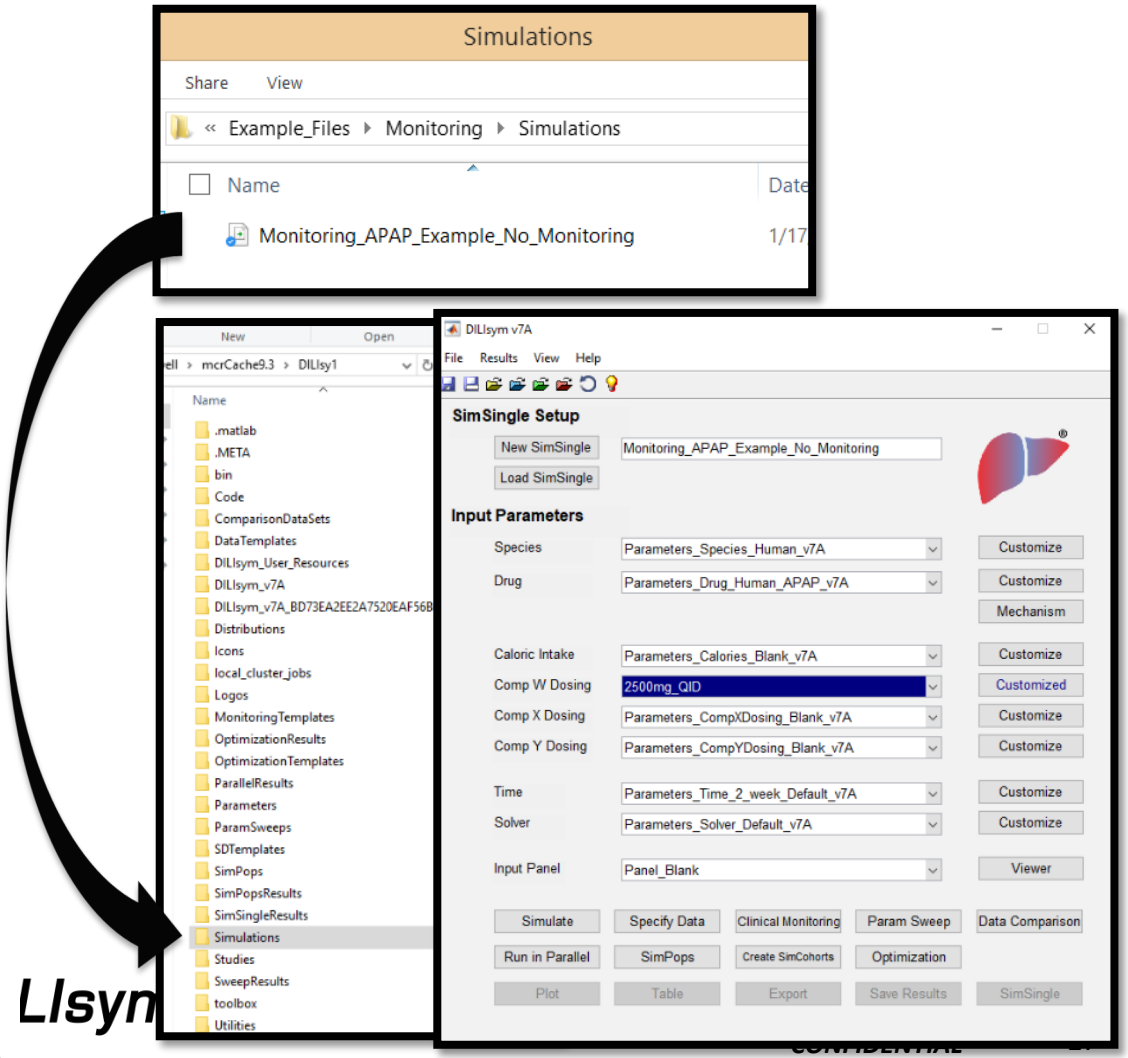




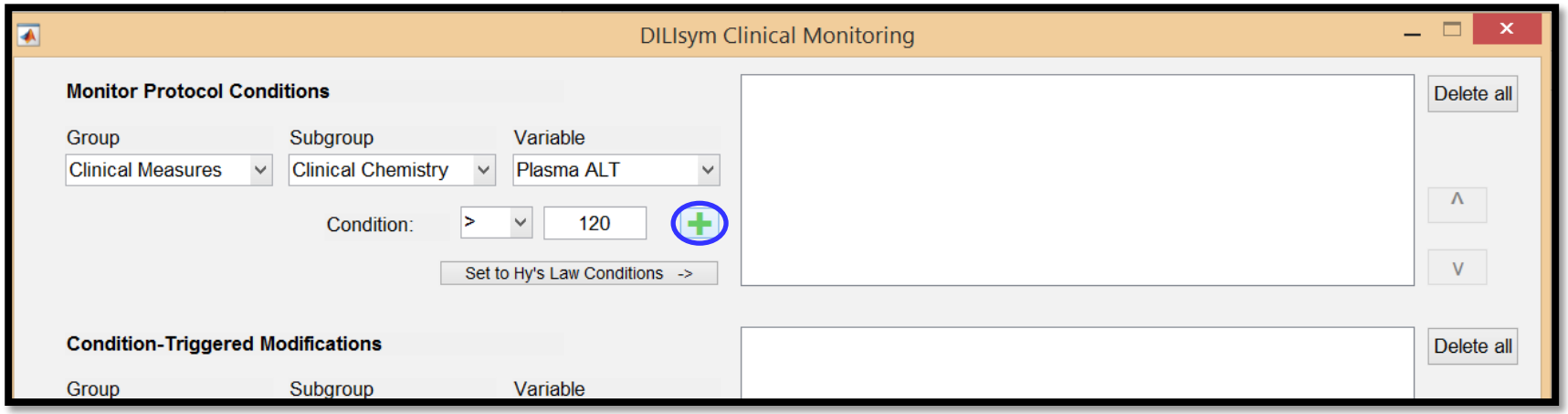
Simulation Results

Hands-on Monitoring Example – *Step 1 – Place Provided SimSingle Setup in Simulations Folder and Review SimSingle*

- Find Simulations directory by clicking any load option within DILIsym and copying location from Windows Explorer
- Copy one provided SimSingle into your Simulations directory
- Explore SimSingle
  - Human species selected
  - Human APAP Drug parameter file
  - No meals (to save simulation time)
  - 2500 mg of Comp W dosed QID for 1 week
  - 2 week simulation time

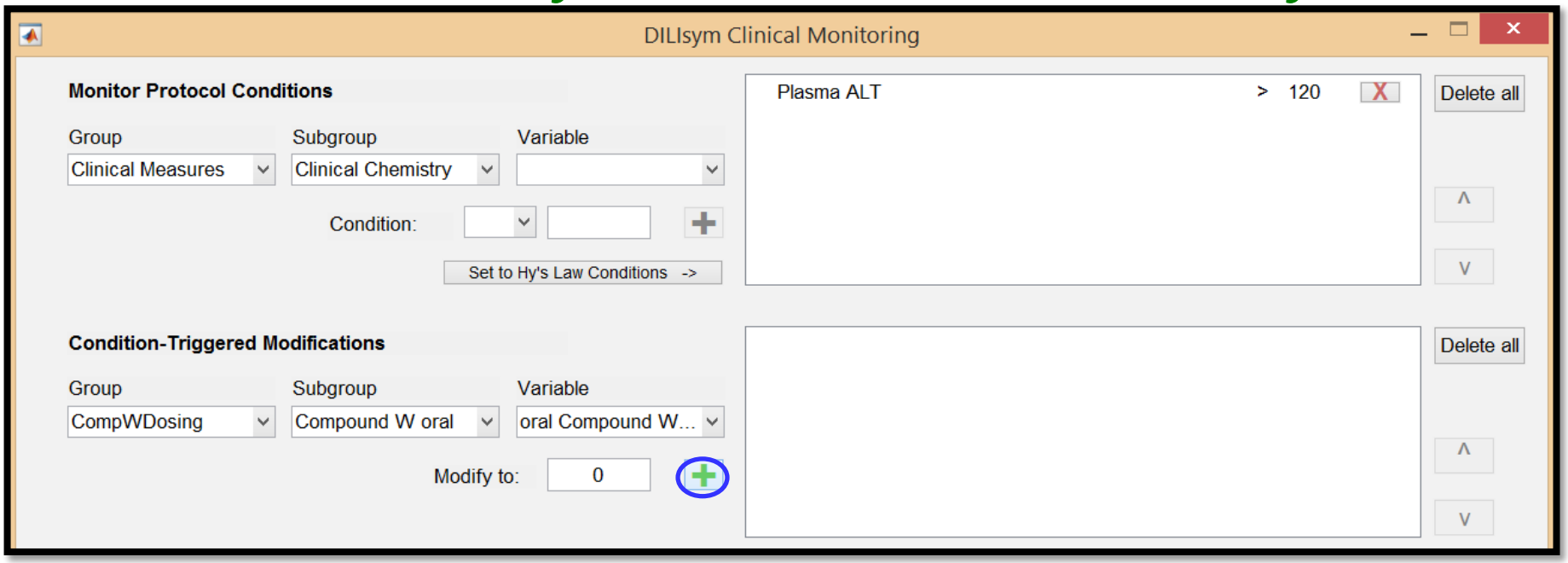


Hands-on Monitoring Example – *Step 2 – Add "Plasma ALT > 120" as Monitored Condition*



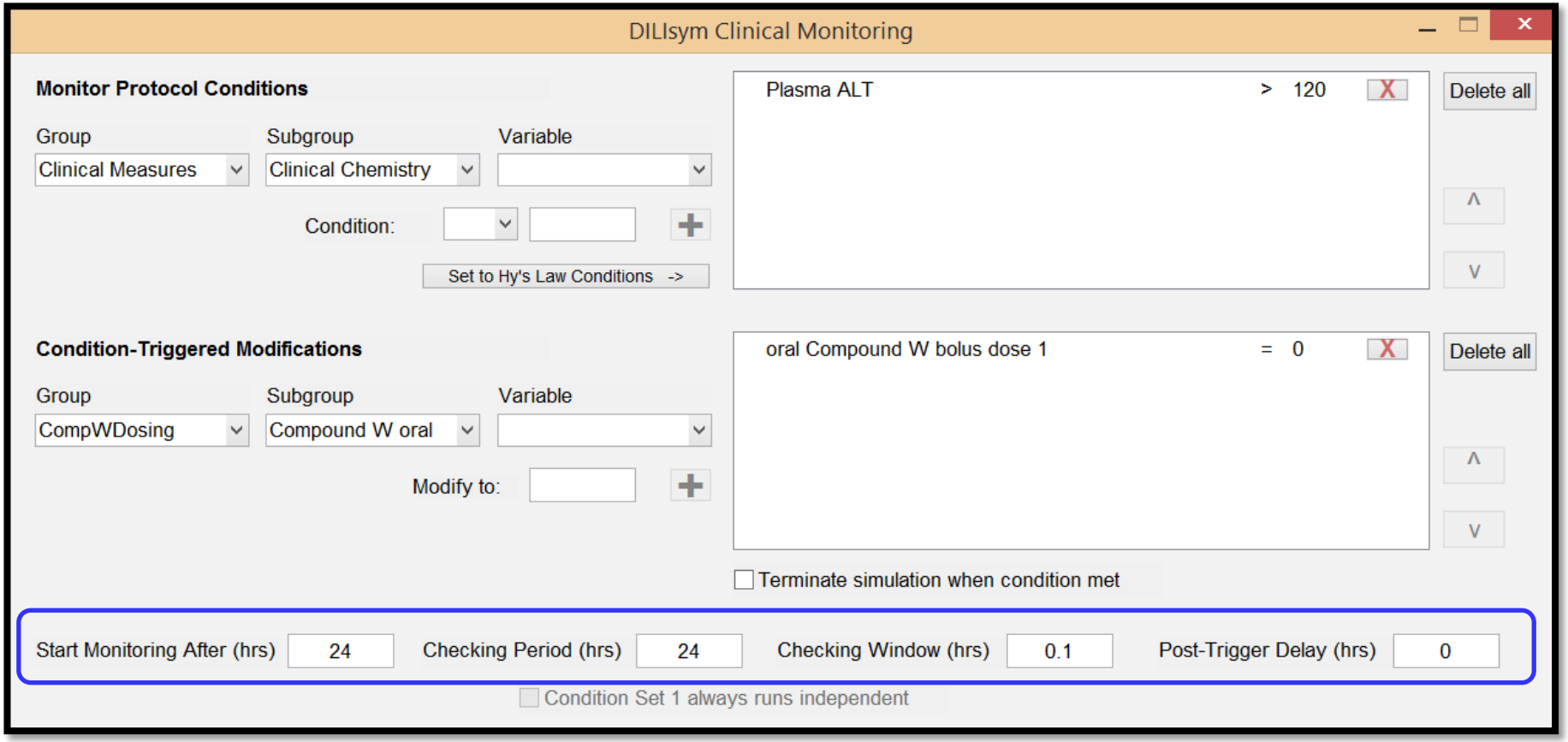
- Open Monitoring interface from DILIsym home screen
  - Select Clinical Measures -> Clinical Chemistry -> ***Plasma ALT*** from drop-down menus
  - Condition: > 120
  - Add monitored condition to table with green "**+**" sign

Hands-on Monitoring Example – *Step 3 – Add "oral Compound W bolus dose 1" as DILIsym Parameter to Modify*



- Add Condition-Triggered Modification
  - Select CompWDosing -> Compound W oral -> ***oral Compound W bolus dose 1*** from drop-down menus
  - Modify to: 0
  - Add modification to table with green "**+**" sign

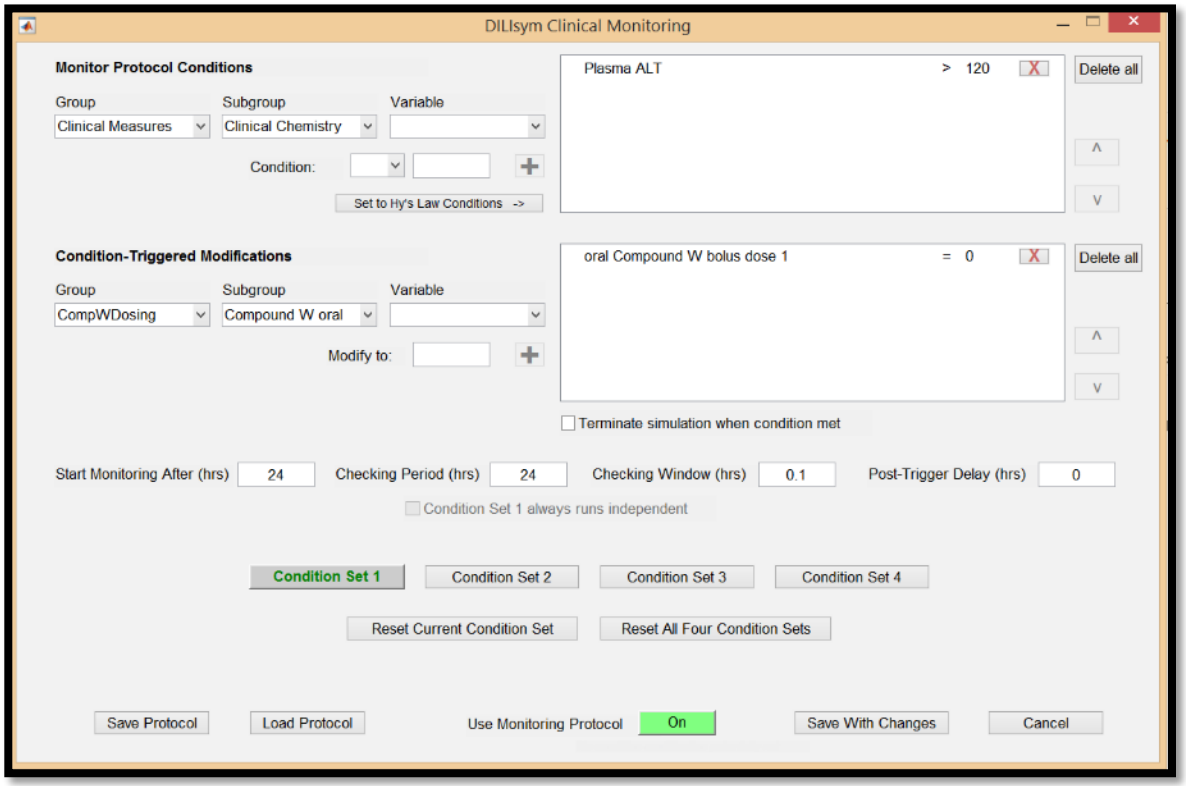
Hands-on Monitoring Example – *Step 4 – Adjust Timing Parameters as Shown*

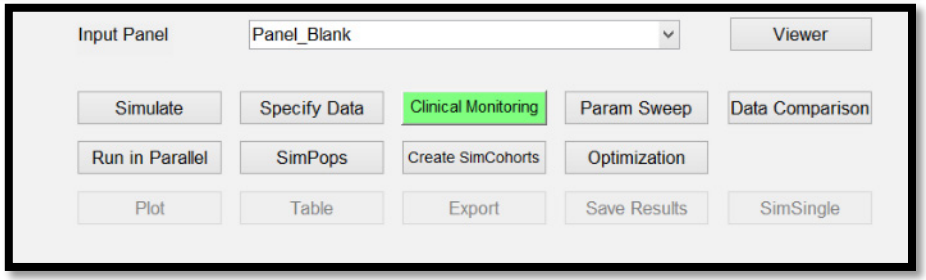


- Start Monitoring After 24 hours
- Checking Period is Daily (24 hours)
- Leave Checking Window at 0.1 hours
- No Post-Trigger Delay

Hands-on Monitoring Example – *Step 5 – Activate Use of Monitoring, Save Setup, and Close*

- DILIsym Monitoring setup should now be fully defined
  - Condition Set 1 button should have **green** text
- Push “Use Monitoring Protocol” button so its green and says “On”
- Save Protocol for use with other SimSingles later
- Close figure by clicking “Save with Changes”
  - Closing figure in other ways, such as “Cancel” button, will not enact the monitoring protocol
- “Clinical Monitoring” Button should now appear green on DILIsym home screen
- Save SimSingle with new name





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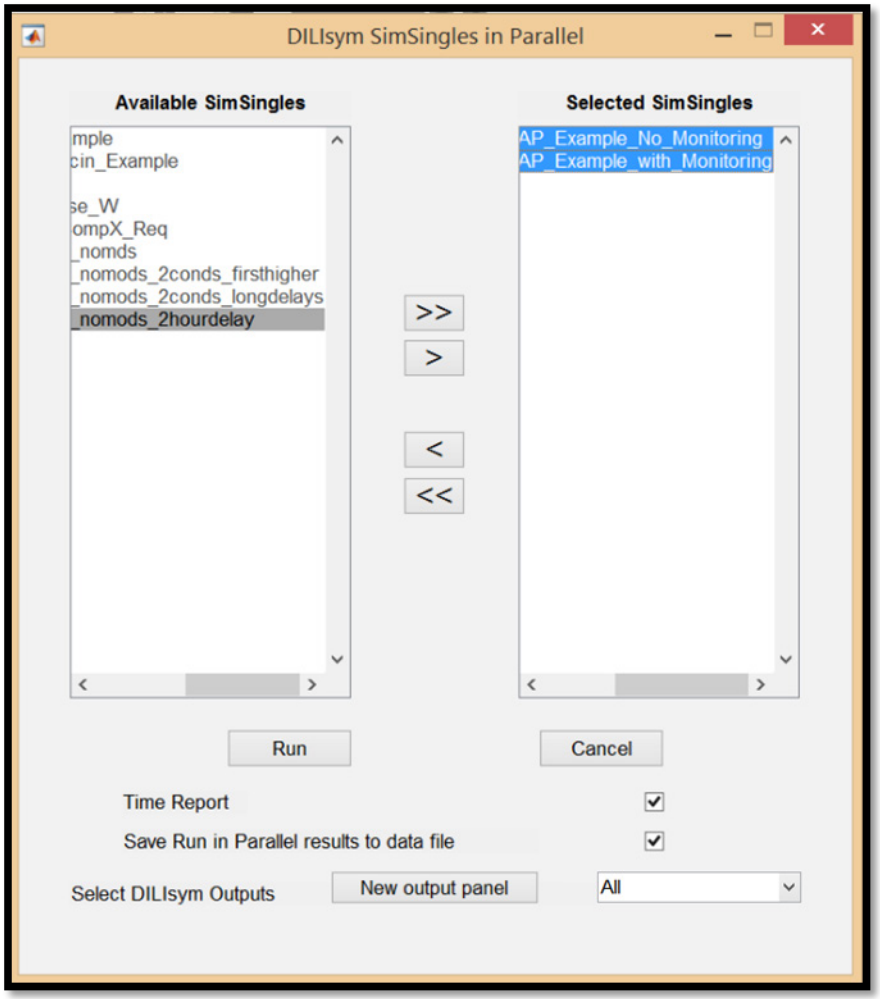
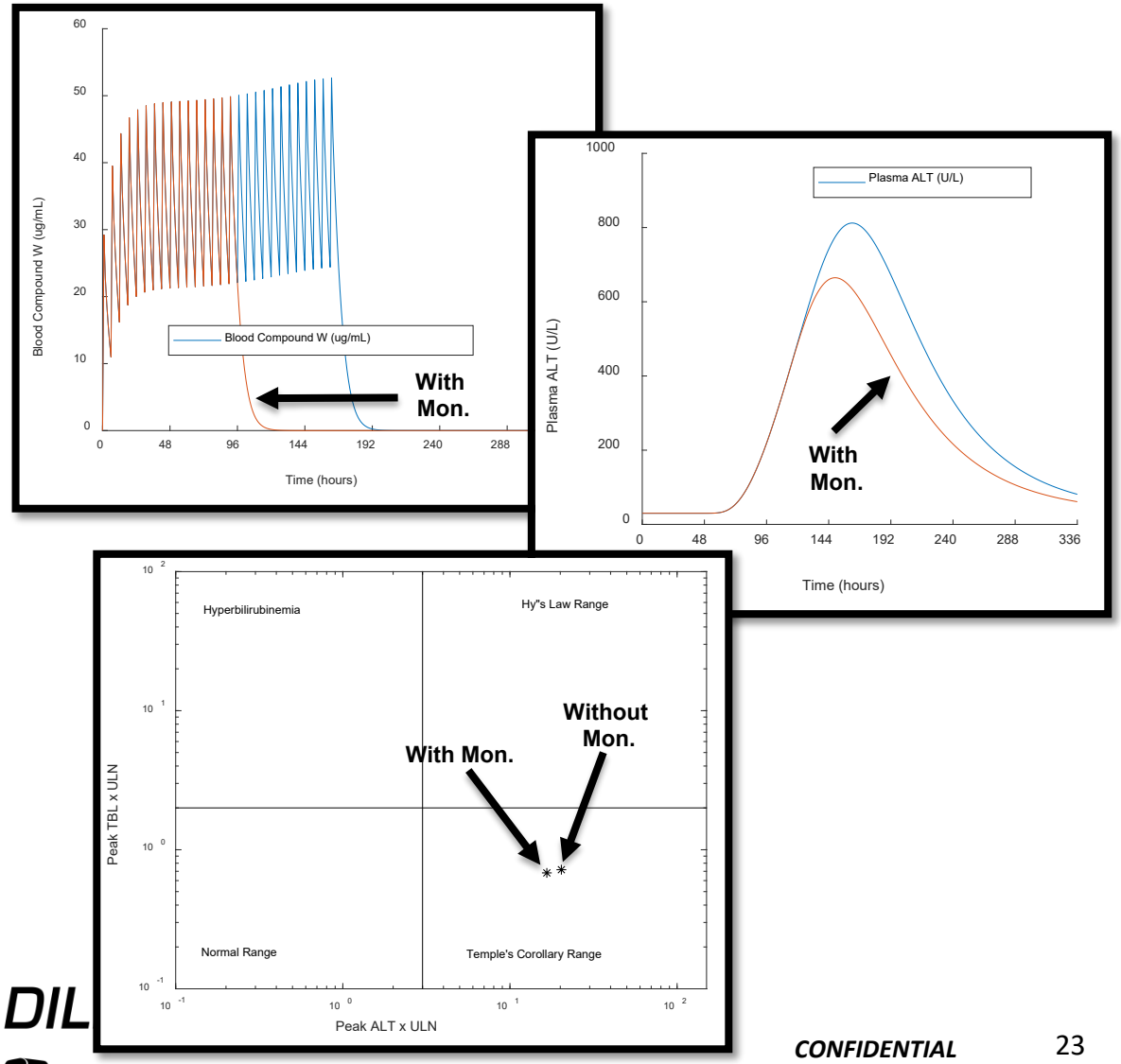
Hands-on Monitoring Example – *Step 6 – Run SimSingles With and Without Monitoring in Parallel*

- Push “Run in Parallel” button from DILIsym home screen
- Add two SimSingles to simulate
  - Original SimSingle provided with no monitoring
  - New, updated SimSingle with monitoring
- Leave DILIsym outputs to save as “All”
- Click “Run”
- Expect 2-4 minutes to complete simulation



Hands-on Monitoring Example – *Step 7 – Compare Results With and Without Monitoring*

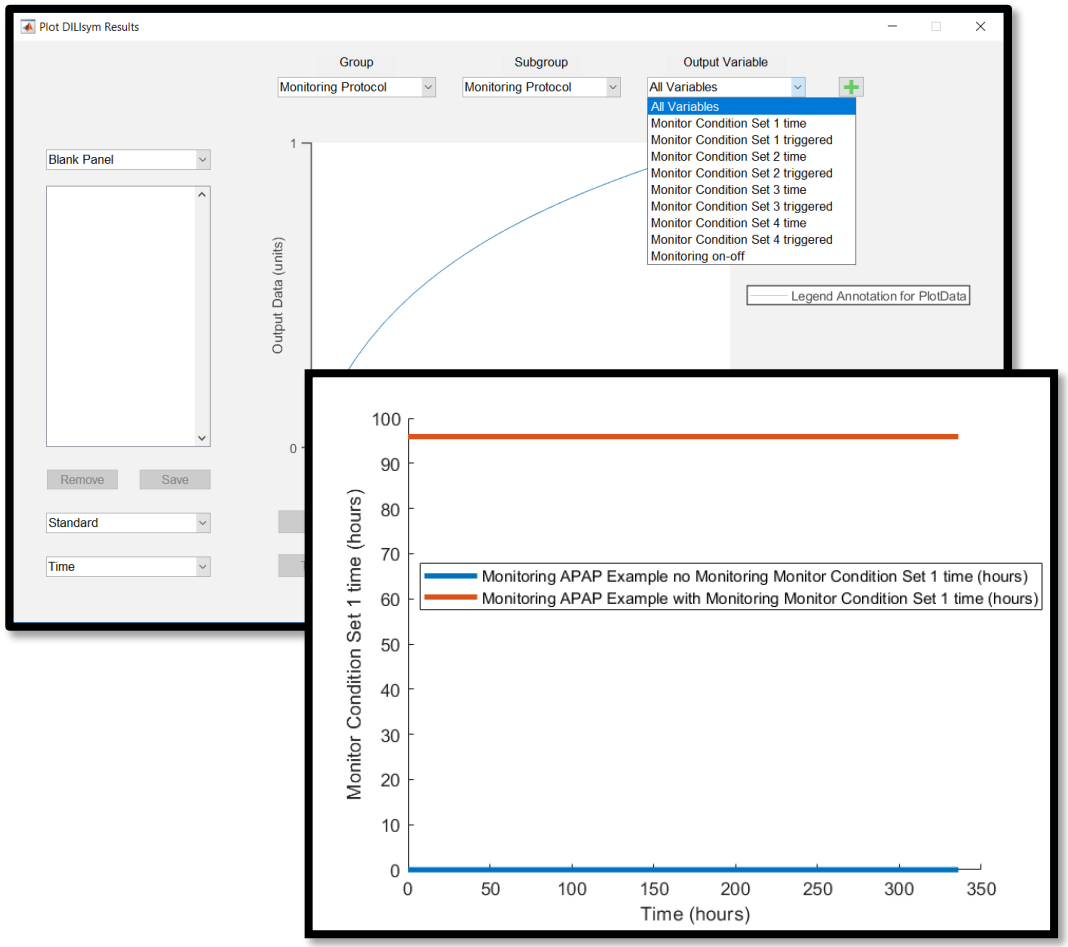
- Open Plot tool within DILIsym and plot these outputs
  - Blood Compound W
  - Plasma ALT
  - eDISH
- Comp W dosing is stopped early with monitoring (red)
- Resulting Plasma ALT peak is lower with monitoring
- eDISH plot also shows this



Simulation Results

Hands-on Monitoring Example – *Step 8 – Examine Monitoring Protocol Variables*

- Open Plot tool within DILIsym and plot these outputs
  - ***Monitor Condition Set 1 time***
- If monitoring has not been triggered (blue), time is 0
- If monitoring has been triggered (red), time that the condition was met is shown



Simulation Results