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DILIsym User Training – Using the DILIsym Monitoring

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

DILIsym Development Team

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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 predefined safety risk threshold
- Typically, when monitoring is conducted during a clinical trial or postmarketing 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 deescalation, 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 realtime 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

<u>Only drug dosing parameters can be changed based on monitoring events</u> <u>in DILIsym v7A</u>

Simulate	Specify Data	Clinical Monitoring	Param Sweep	Data Comparison
Run in Parallel	SimPops	Create SimCohorts	Optimization	
Plot	Table	Export	Save Results	SimSingle

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

DILIsym Monitoring Interface User specifies what to monitor and what to do if specified event is triggered

DILIsym Solver Call Function Controls the starting and stopping of the differential equation solver

DILIsym Differential Equations and Algebraic Expressions Mathematics behind the simulations

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DILIsym Events Function Checks for presence or absence of occurred events



DILIsym Monitoring Tool – Critical Components

- 1. <u>SimSingle (simulation setup) within DILIsym via the home screen</u>
 - 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. <u>Specification of monitoring conditions using the DILIsym Monitoring</u> <u>interface for Condition Set 1</u>
 - 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)



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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	DILIsym Clinical Monitoring – 🗆 🗙
4. Condition Set buttons	Monitor Protocol Conditions Group Subgroup Variable Condition: Condition: Set to Hy's Law Conditions ->
	Condition-Triggered Modifications Delete all
Simulate Specify Data Clinical Monitoring Param Sweep Data Co Run in Parallel SimPops Create SimCohols Optimization Plot Table Export Save Results Sim Image: Simple Land Strömgere Input Parameters Frank Simple Control Simple Cont	Modify to: Terminate simulation when condition met Start Monitoring After (hrs) 0 Checking Window (hrs) 0.1 Post-Trigger Delay (hrs) 0
Species Parametern_Species_Ikmas_u7A Colomice Dog Parametern_Datg_Bank_u7A Colomice Culoric Intale Parametern_Colorite_Blank_u7A Colomice Culoric Intale Parametern_Colorite_Blank_u7A Colomice Comp V Dosing Parametern_Colorite_Blank_u7A Colomice Comp V Dosing Parametern_CompXDosing_Blank_u7A Colomice Trive Parametern_Eore/Dafad_u7A Colomice Parametern_Blank_u7A Colomice Colomice Imput Parel Parel_Blank Vereer Smulate Specify Data Once Montanian Parametern_Datametern	Condition Set 1 always runs independent Condition Set 1 Condition Set 2 Condition Set 3 Condition Set 4 Reset Current Condition Set Reset All Four Condition Sets Save Protocol Load Protocol Use Monitoring Protocol Off Seve With Changes Cancel No condition-modification pairs fully set
Run in Parallel SimPops Come tencionet Optimization Plot Table Export Sime Results SimSingle	CONFIDENTIAL

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Add Your Intended Condition Set 1 Monitoring Conditions

•			DILIsym (Clinical Monitoring -	- 🗆 🗙
	Monitor Protocol Condi	tions			Delete all
		Subgroup	Variable		
	~	~	~		Δ
		Condition:	× +		
		Set t	o Hy's Law Conditions ->		V

- 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)

Condition-Trig	gered Modifications				Delete al
Group	Subgroup	Variable	_		
	~	Modify to:	+		۸
					V
				Terminate simulation when condition met	

- 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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The Condition Set Buttons Allow Toggling Between Different Condition Sets

Condition Set 1	Condition Set 2	Condition Set 3	Condition Set 4
Res	et Current Condition Set	Reset All Four Condition	on 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 <u>green</u>
- 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

Condition Set	Condition Set 2	Condition Set 3	Condition Se	t 4				
	Reset Current Condition Set	Reset All Four Condition	on Sets					
Save Protocol Load Protocol	Use Monitoring Proto	ocol On	Save With C	changes	Cancel			
							~	Viewer
				Simulate	Specify Data	Clinical Monitoring	Param Sweep	Data Comparison
				Run in Parallel	SimPops	Create SimCohorts	Optimization	
				Plot	Table	Export	Save Results	SimSingle

- 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

	Simulations			
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DILIsym_v7A	Drug	Parameters_Drug_Human_APAP_v7A	~	Customize
DILIsym_v7A_BD73EA2EE2A7520EAF5	i6B			Mechanism
Distributions				
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local_cluster_jobs	Comp W Dosing	2500mg_QID	\sim	Customized
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OptimizationResults				
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ParallelResults	Time	Description Time 2 work Default of		Customize
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ParamSweeps	Solver	Parameters_Solver_Default_v7A	\sim	Customize
SDTemplates				
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toolbox Utilities				
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Hands-on Monitoring Example – Step 2 – Add "Plasma ALT > 120" as Monitored Condition

DILIsym Clinical Monitoring	- • ×
Monitor Protocol Conditions	Delete all
Group Subgroup Variable	
Clinical Measures V Clinical Chemistry V Plasma ALT V	
Condition: > v 120	Λ
Set to Hy's Law Conditions ->	V
Condition-Triggered Modifications	Delete all
Group Subgroup Variable	

- 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



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

DILIsym C	Elinical Monitoring —	□ ×
Monitor Protocol Conditions	Plasma ALT > 120 X	Delete all
Group Subgroup Variable Clinical Measures Clinical Chemistry Condition: Set to Hy's Law Conditions ->		∧ V
Condition-Triggered Modifications Group Subgroup Variable		Delete all
CompWDosing Compound W oral oral Compound W Modify to: 0 (+) (+)		∧ ∨

- 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

DILIsym Cl	inical Monitoring	-	- 🗆 ×
Monitor Protocol Conditions	Plasma ALT	> 120 🔀	Delete all
Group Subgroup Variable Clinical Measures Clinical Chemistry Condition: Set to Hy's Law Conditions ->			∧ V
Condition-Triggered Modifications Group Subgroup Variable CompWDosing Compound W oral Modify to:	oral Compound W bolus dose 1	= 0 🗙	Delete all
	Terminate simulation when condition met		
Start Monitoring After (hrs) 24 Checking Period (hrs) 24	Checking Window (hrs) 0.1	Post-Trigger Delay (hrs)	0

- 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

]	C	ILIsym Clinical Moni	toring		_ 🗆 ×
Monitor Protocol Conditions Group Subgroup	Variable	Plasma A	LT	> 1	20 X Delete all
Clinical Measures V Clinical Chemis	stry v	~			
Condition:	Set to Hy's Law Condition	+			∧ V
Condition-Triggered Modifications		aral Com	oound W bolus dose 1	= 0	X Delete all
		orai Com	Dound vy bolus dose 1	= (Delete all
Group Subgroup	Variable				
CompWDosing Compound W	Modify to:	+			∧ V
		Terminate	simulation when condition	met	
Start Monitoring After (hrs) 24	Checking Period (hrs)	24 Checkin Set 1 always runs indep	g Window (hrs) 0.1	Post-Trigger De	lay (hrs) 0
Condit				ondition Set 4	
	Reset Current Con	dition Set Res	et All Four Condition Sets		
Save Protocol Load Pro	tocol Use	Monitoring Protocol	On S	ave With Changes	Cancel
				oro mangoo	- Cullou
	Input Panel	Panel_Blank		~	Viewer
	Simulate	Specify Data	Clinical Monitoring	Param Sweep	Data Comparison
	Run in Parallel	SimPops	Create SimCohorts	Optimization	
	Plot	Table	Export	Save Results	SimSingle

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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

DILIs	ym SimSingles in F	Parallel	- • ×
Available SimSingles		Selected SimSi	ngles
mple cin_Example se_W ompX_Req _nomds _nomods_2conds_firsthigher _nomods_2conds_longdelays _nomods_2hourdelay	>> >> >> >> >> >> >> >> >> >> >> >> >>	AP_Example_No_Mo AP_Example_with_Mo	nitoring nitoring
Run Time Report Save Run in Parallel resu Select DILIsym Outputs	ults to data file New output panel	< Cancel	>

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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



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