ReadMe Notes

1. *What's New in East 5*

East 5 upgrades the East system in several important ways in direct response to customer feedback. Six important extensions have been developed in East 5:

1.1. **Designs using t-tests:**

In previous versions of East, the single look design was treated as a special case of a group sequential design. Thus the same large sample theory was used to power and size these traditional types of designs. Recognizing this solution not to be entirely satisfactory for small sample trials, in East 5, we have implemented single-look t-test designs for continuous data. (Sections 8.1.4, 8.2.4, 9.1.3, and 11.1.3)

1.2. **New boundaries:**

East 5 provides two new procedures for specifying group sequential boundaries. Generalized Haybittle-Peto boundaries allow the user to specify unequal p-values at each interim look for a group sequential plan. East will recalculate the final p-value in order to preserve the type I error. (Section
38.1) The cells for entering the cumulative alpha values of an interpolated spending function can be automatically populated with the cumulative alpha values of any of the published spending functions available to East, and subsequently edited to suit user requirements. For example, a 4-look Lan and DeMets O'Brien-Fleming spending function can be modified so
that the critical value at the first look is less conservative than usual. (Section 38.3.1)

1.3. **Interim monitoring and simulation for single-look designs:**

Interim monitoring and simulation sheets have been provided for all single look designs in East 5.

1.4. **Improvement to Charts:**

Many improvements to existing charts in East have been implemented in this version. Scaling in the Duration vs. Accrual chart has been corrected to provide a better tool for the user. The use of semi-log scaling has enabled us to represent many charts on the natural scale of the treatment effect. This concerns mostly any ratio and odds ratio metrics such as the relative risk, the hazard ratio, and the odds ratio. Boundaries on the relative risk scale for example are now available in East 5. Boundaries can also be visualized on the score scale. Charts can be summarized in tabular form. Option is given to the user to generate tables of power vs. sample size, power vs. treatment effect, events vs. time, and so on. These tables can easily be copied and pasted into external applications like Microsoft Word and Excel (Section 4.5).

1.5. **Improved usability:**

Much attention in East 5 was spent to improve the user's experience within the environment. A graph sheet allows the user to compare up to 16 charts side by side. Charts for any number of plans within a workbook can be exported to the graph sheet. (Section 5.3) The scratch sheet is a full-fledged Microsoft Excel sheet that can be brought up within the East application. (Section 4.4) The split view option enables the user to see two sheets of the same workbook simultaneously. This can be useful if one window pane contains a scratch sheet where side calculations may be done based on numbers in the other window pane. Another use can be to have two or plans to show up on one pane and their graphsheet containing boundaries or other charts to show up on another pane

for easy comparison. (Section 4.8) Messages in the help menu, pop-up help, and context sensitive help have been revised and rendered more informative to the user. The default appearance of charts can be specified by the user through the preferences settings menu item. (Section 4.7)

1.6. **Installation validation:**

East 5 includes an installation validation procedure that will easily check that the software has been properly installed on the user's system. (Section 2.3)

Finally, there has been an important reorganization of the East manual, which now comprises seven volumes organized as follows: (1) The East System (2) Continuous Endpoints (3) Binomial and Categorical Endpoints (4) Time-to-Event Endpoints (5) Adaptive Designs (6) Special Topics (7) Appendices. Page numbers are continuous through volumes 1-7. Each volume contains a full table of contents and index to the whole manual set.

2. What's New in East 5.1

EastSurv: Important improvements have been made to the EastSurv module. As a consequence, important changes and updates have been made to Volume 4 of the East 5 Manual set. Four major improvements are listed below (Refer to Chapters 28 and 29 of the Online Manual or Chapters 4S-1 and 4S-2 of Vol. 4 of the Printed Manual).

2.1. **Survival designs given accrual duration and study duration**:

Previous versions of East asked the user to specify the accrual rates and one of either the sample size or the accrual duration before calculating the study duration as an output. With the new designs (superiority and non-inferiority) available in EastSurv with East 5.1, the user is asked the accrual duration and the study duration. East then calculates the sample size required to properly power the study. The assumption is that the sponsor will open however many study centers are required to meet the recruitment goals.

2.2. **New survival and drop-out information input and variable drop-outs**:

New methods of entering survival and drop-out information – such as median survival times or cumulative drop-outs - have been made available in the new EastSurv to facilitate trial design.

Also, survival designs can now incorporate non-uniform drop-out rates in each treatment arm.

2.3. **Computing power and power charts**:

The new survival designs given accrual duration and study duration allow East to compute power for a given sample size, something not previously available.

In addition, new charts of Power vs. sample size, number of events, accrual duration, or study duration have been made available.

2.4. **Improved survival simulations**:

The user interface for survival simulations has been completely revamped, with a more logical grouping of the information displayed and new input and output options. Simulation data for instance can be saved to a user-specified file; boundaries are recomputed upon changing the information fraction of the looks. Please refer to the relevant section of the updated manual for an explanation of these new capabilities.

3. *Fixes and Improvements*

- Computations in survival module have improved accuracy in East 5 compared to East 4.
- Haybittle-Peto boundary computations are more accurate in East 5 than in East 4.
- A bug in East 4 relating to computing MSE in procedures for "Normal-Equivalence-Crossover" designs has been fixed in East 5.
- In Adative designs, ACR method has been removed in East 5, as this method has problems in preserving type-1 error.
- In survival Non-inferiority procedures, the definition of hazard ratio has been changed to lambda_t/lambda_c, which was the reverse in East 4.
- Under certain situations, the CHW calculator computed wrong sample size. This has been fixed
- Under Direct Monitoring, the two sided p-value was not correct. This has been fixed.
- NLP computation was incorrect in the case of
  a) one-sided superiority design with negative effect size and HP boundaries and
  b) non-inferiority design with positive effect size and HP boundaries.

This has been fixed now. This fix also affects the conditional power and post-hoc power computations. Files saved with these input combinations need to be opened again for re-computations.

- In the case of Survival designs with alternative variance, computation of maximum study duration was incorrect when maximum value was used for accrual duration or accrual subjects. This has been fixed now. In such cases, maximum number of events, expected study duration, expected number of events and expected sample size computations are also affected.
- The "View Data" feature of "Events / Accruals vs. Time" chart showed incorrect numbers in the case of variable hazard rates. This has been fixed now.

4. Installing East 5.1

System Requirements to run East 5.1

The minimum hardware/operating system/software requirements for East 5.1 are:

A system running one of the following operating systems:

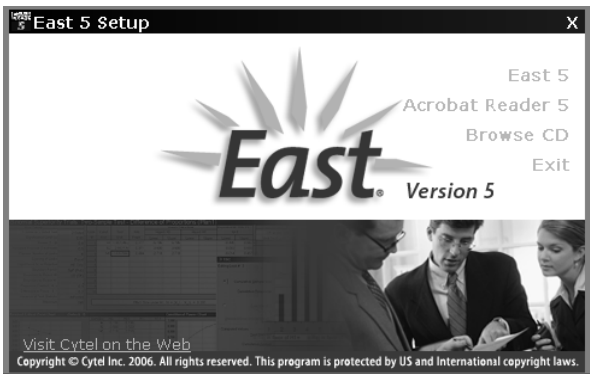
- Windows 2000/XP
  - A minimum of 256 MB RAM (512 MB recommended)
  - A hard disk with at least 25 MB of free disk space
  - Microsoft Excel 2000 SR-1 or 2002 or 2003 version.

Installation

To install East 5.1, please follow these steps:
i) If an earlier (including beta and demo) version of East 5 is currently installed on your PC, please uninstall it or else the installation of the current version will not proceed correctly. To
uninstall the earlier version of East 5, go to the Start Menu and select:

Programs-> East 5-> Uninstall East 5

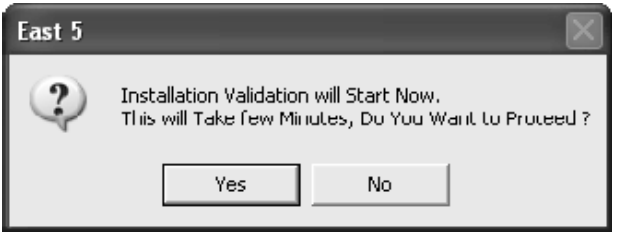
ii) Insert the East 5.1 CD into your CD-drive.
(a) If your Windows Auto run Default is already active, you'll see an installation screen similar to what is shown below. Follow the instructions that will appear on the screen.



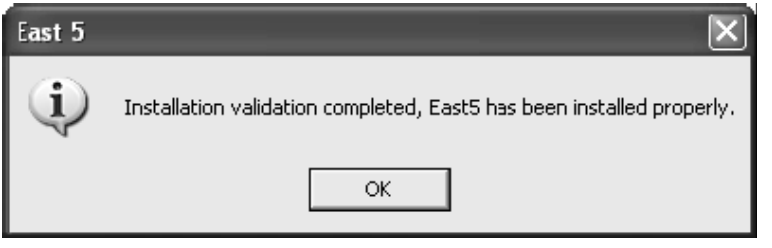
(b) If your Windows Autorun Default is not active, you won't see any installation screen. In that case, open your Windows Explorer, click on the CD Drive, and double-click on Setup. Then you will see the installation screen. Follow the instructions that will appear on the screen.

5. Validating Installation

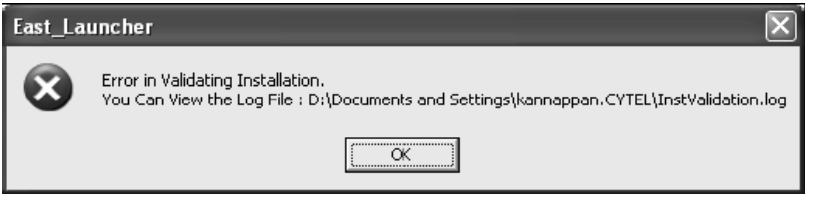
To validate installation of East 5.1, go to the Start Menu and select
Programs-> East 5.1-> Validate Installation.
You will be presented with the following dialog box.



Click on Yes. If the installation validation is successful, you will get the following message box



Click on OK.
If the installation validation is not successful, you will get a message similar to the one shown in the following message box.



Click on OK and then send the log file InstValidation.log to support@cytel.com for getting help on the installation validation failure.

6. Errata in Manual

East 5 Manual: Volume 7 : Appendices: Appendix A. Section A.5.
Please read equation (A.88) as shown below.

$$E(l|a,S_a,\lambda)=\begin{cases} a[l-\frac{1-e^{-\lambda l}}{\lambda}] & \text{if } l\le S_a \\ a[S_a-\frac{e^{-\lambda l}}{\lambda}(e^{\lambda S_a}-1)] & \text{if } l>S_a \end{cases}$$

Please read the explanatory note for equation (A.89) to be as shown below.

$E(l|a,S_a,\lambda,\gamma,m)$ = expected number of events at calendar time l given

a: a vector of enrollment rates for different intervals in the enrollment phase;
S_a: a vector of enrollment durations corresponding to the components of a;
λ: a vector of hazard rates for piece-wise exponential survival;
γ: a drop-out rate for subjects lost to follow-up;
m: a fixed follow-up time for each subject ($m=\infty$ denotes variable follow-up).

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