



esubpack: R package to facilitate regulatory review

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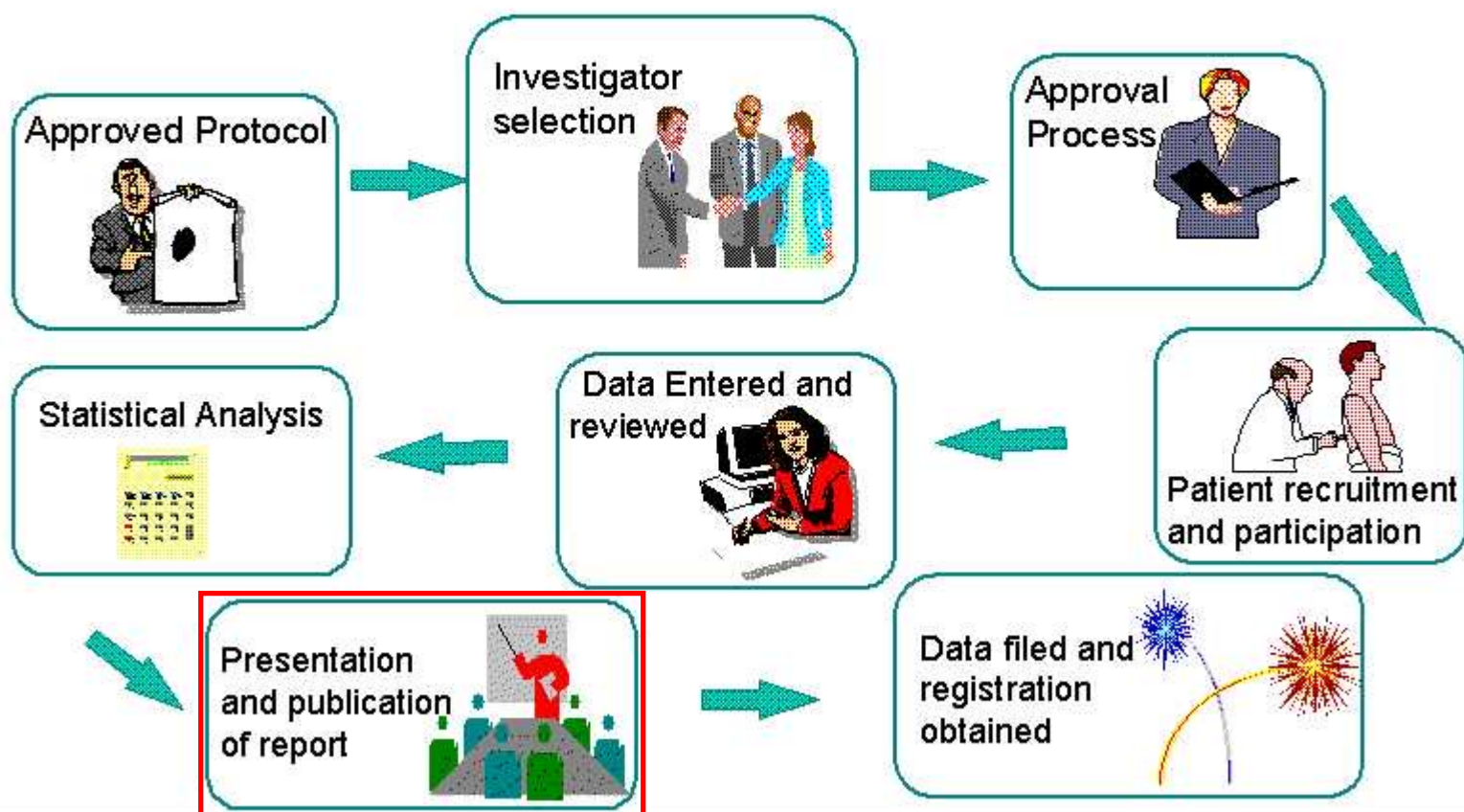
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Introduction: Clinical Trials Lifecycle

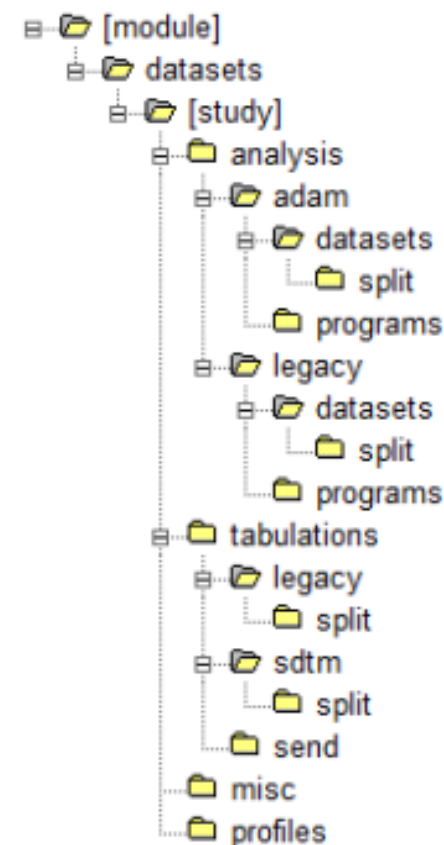
Clinical Trials in a Nut Shell



Introduction: Electronic Submission Format

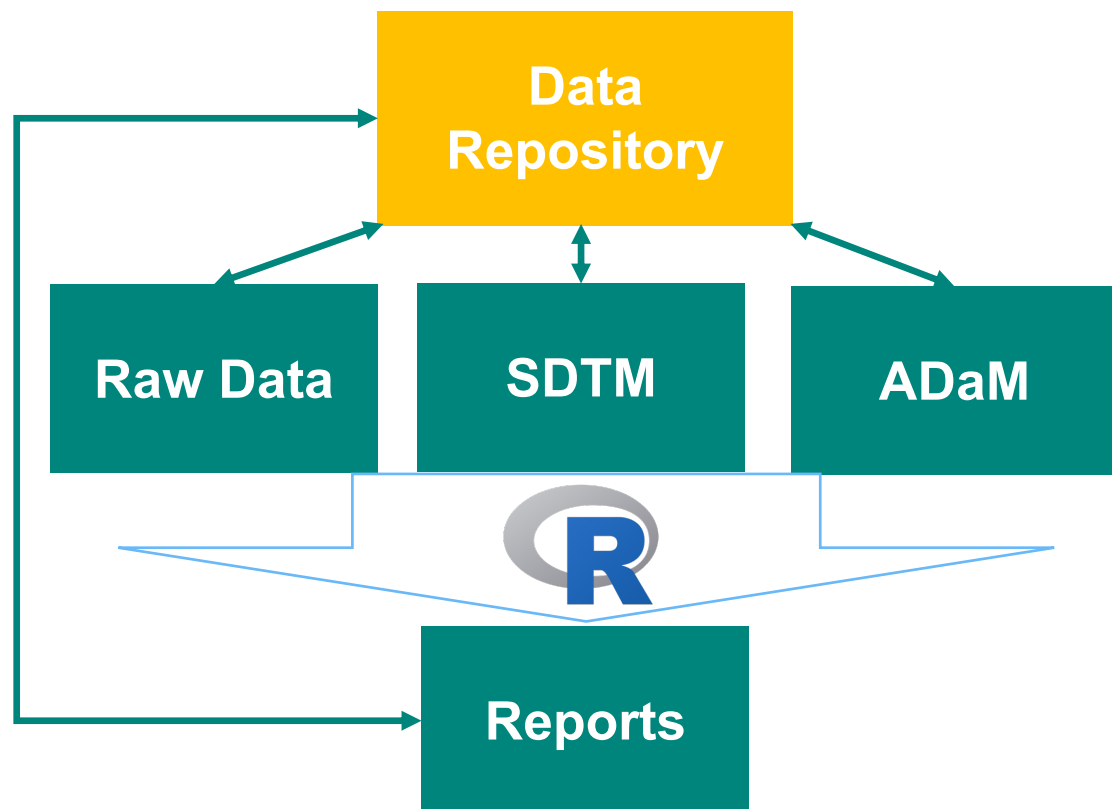
The electronic Common Technical Document (eCTD) is a standard format for the electronic submission of applications, amendments, supplements, and reports from the applicant to the regulator.

Electronic File Directory

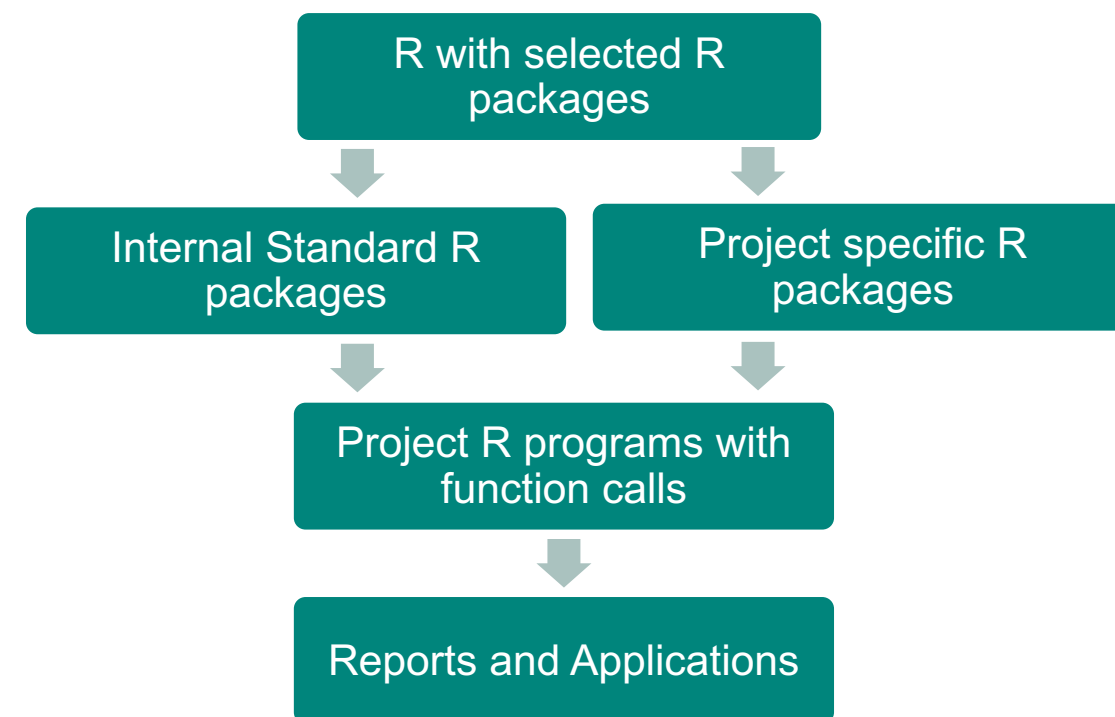


Introduction: R Usage in A&R

R usage in Clinical trials A&R



R Development Structure



Introduction: Problem Statement

Following requirements are summarized from section 4.1.2.10 of the [FDA Study Data Technical Conformance Guide](#)

- Software programs used to create all ADaM datasets, tables, listings and figures (TLFs) are required to be submitted.
- Traceability is required and reviewer need to be able to reproduce the analysis results with proper instructions.
- Software programs should be submitted in ASCII text format.
- Executable file extensions should not be used.

Introduction: Overview of esubpack

- An R package that enables reproducibility of the environment used by the sponsor to prepare eCTD deliverables for the regulatory reviewers.
- Creates portable R environment on reviewer's computer in a chosen folder for review of analysis & reporting deliverables included in the submission.
- esubpack offers ability to copy necessary data files to the chosen folder.

Dependencies of esubpack

- esubpack uses the following R packages
 - fs
 - stringr
 - pkglite
 - cleanslate
 - brew
 - haven
- pkglite and cleanslate are the two main dependencies used.
- All dependencies except cleanslate are available on the CRAN.

Dependencies of esubpack: pkglite

- pkglite converts one or more source packages to an ASCII text file enabling submission through the FDA eCTD gateway and restores the package structure from the files to enable reviewers to reproduce the results.
- Package website: <https://merck.github.io/pkglite/>
- pkglite is available on CRAN and was used in R Consortium R submission pilot 1 and pilot 2 to the FDA.
 - [R Submissions Working Group - Background \(rconsortium.github.io\)](https://rconsortium.github.io/)
- Installation: `install.packages("pkglite")`

Dependencies of esubpack: pkglite

Code to Pack an R package:

```
library("pkglite")

pkg <-
system.file("examples/pkg1",
package = "pkglite")

txt <- tempfile(fileext = ".txt")

pkg %>%
  collate(file_default()) %>%
  pack(output = txt, quiet = TRUE)
```

First few lines of the output TXT file:

```
# Generated by pkglite: do not edit by hand
# Use pkglite::unpack() to restore the packages

Package: pkg1
File: DESCRIPTION
Format: text
Content:
  Package: pkg1
  Type: Package
  Title: Example Package One
  Version: 0.1.0
```

Dependencies of esubpack: pkglite

Code to Unpack an R package:

```
out <- file.path(tempdir(),
"onepkg")

txt %>% unpack(output = out, quiet
= TRUE)
```

Output:

This will create a directory named after the R package under the output directory

Code to display files in the folder:

```
out %>%

  file.path("pkg1") %>%

  list.files()
```

Output:

```
[1] "data"      "DESCRIPTION" "man"      "NAMESPACE"
[5] "NEWS.md"   "R"           "README.md" "vignettes"
```

Dependencies of esubpack: cleanslate

- The aim of cleanslate package is to create portable R environment.
- It supports:
 - Creating a project folder with project-specific context (.Rproj, .Rprofile, .Renviron)
 - Installing a specific version of R into the project folder
 - Installing a specific version of Rtools into the project folder
- Our primary focus is Windows while the other platforms can be added in future versions.
- Cleanslate is still under development and will be open-sourced later.

Dependencies of esubpack: cleanslate

Code to Create a portable R environment:

```
library("cleanslate")

"C:\temp\" %>%
  use_project() %>%
  use_rprofile() %>%
  use_renvir() %>%
  use_r_version(version = "4.1.1")
%>%
  use_rtools(version = "rtools40")
```

This will:

- Create a project folder under C:/temp/ with a .Rproj file;
- Create a .Rprofile file under the project folder, set options(repos) to use the specified repo and give instruction to set the R binary path in RStudio IDE;
- Create a .Renvir file under the project folder and set the library path to be the library of the project-specific R installation.
- Download R 4.1.1 installer from CRAN, and install it into C:\temp\R\;
- Install rtools40 from CRAN, and install it into C:\temp\Rtools\;

Workflow of esubpack

Step 0: Prerequisites

- The submission ready deliverable project has already been packed using pkglite and submitted by the sponsor.
 - ☐ A text file named r0pkgs.txt and programs in text format are assumed to be present in the source folder.
- esubpack can be only used on Windows environment now, please ensure the paths are Windows compatible and are not based on any cloud service provided paths.

Workflow of esubpack

Step 1: Specify user input paths for eSubmission related deliverables

Reviewer runs `check_source()` to pass desired parameters to initiate setup, this function needs to be run first before calling any other functions in the package.

```
source_params <- check_source(  
  path_source = file.path(Sys.getenv("USERPROFILE"), "R/test/programs"),  
  path_dryrun = file.path(Sys.getenv("USERPROFILE"), "R/esub"),  
  path_adam = file.path(Sys.getenv("USERPROFILE"), "R/test/adam"),  
  path_sdtm = file.path(Sys.getenv("USERPROFILE"), "R/test/sdtm"),  
  src_reposnap = c("https://packagemanager.posit.co/cran/2021-10-19"),  
  src_rversion = c("4.1.1"),  
  req_pkgs = c("tidyverse", "r2rtf", "pkglite", "emmeans", "haven",  
"stringr"),  
  skip_disp = FALSE)
```

Workflow of esubpack

Step 2: Create portable R environment

Reviewer runs `use_esub_project()` to create portable R environment at path indicated in `check_source()` function call.

Since the paths have already been defined in the previous step, we call `use_esub_project()` simply using `source_params` object as input.

```
use_esub_project(source_params)
```

Manual Step:

After the new R environment is created, reviewers need to change the setting of R path to the installation path manually in RStudio.

Workflow of esubpack

Step 3: Unpack submission package

Reviewer runs `use_esub_unpack()` function to install R packages required for analysis from defined R package snapshot path, copy necessary files to eSub folder path indicated in the `check_source()` function and unpack the deliverables by converting text files submitted by the sponsors to R script files.

```
use_esub_unpack(  
  source_params,  
  file_type = c("txt"),  
  copy_data = c("BOTH"),  
  skip_disp = FALSE)
```

Workflow of esubpack

Demo:

The demo will use the data from Pilot1 Submission of R Consortium, which is available on GitHub.

Repository link: <https://github.com/RConsortium/submissions-pilot1>

Conclusion

Conclusion:

- esubpack enables submission of programs used to generate A&R deliverables in R through FDA submission gateway
- esubpack creates a portable R environment with all the dependencies to facilitate regulatory review with full reproducibility.

Future Work:

- External release of esubpack and cleanslate to CRAN
- Enable use within other common operating systems apart from Windows

Awesome Team!



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Thank you



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