# Reproducible Pharmacometrics

## Using Reproducible Research methodologies to improve pharmacometric analyses

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SGS Exprimo  Pharmetheus

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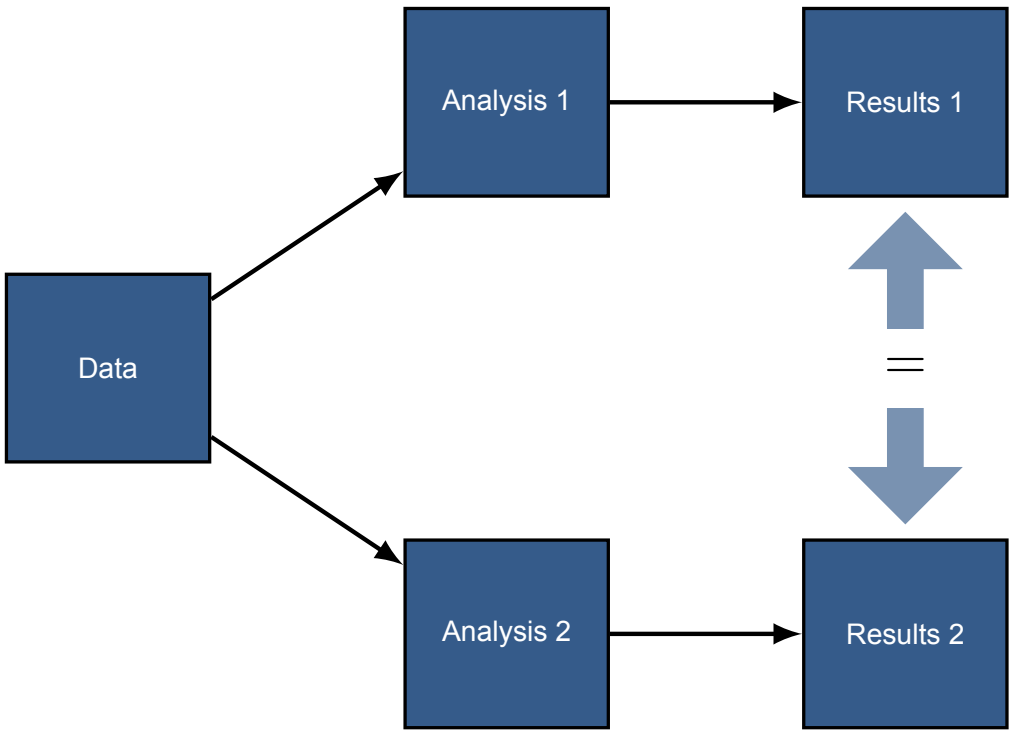
# The aim

- To show how the principles of Reproducible Research can be used to improve quality and efficiency of generating pharmacometric Results (slides, reports and manuscripts).
- To show how recent advances in open software support the implementation of Reproducible Research workflows in pharmacometric analyses.

# Reproducibility and Reproducible Research



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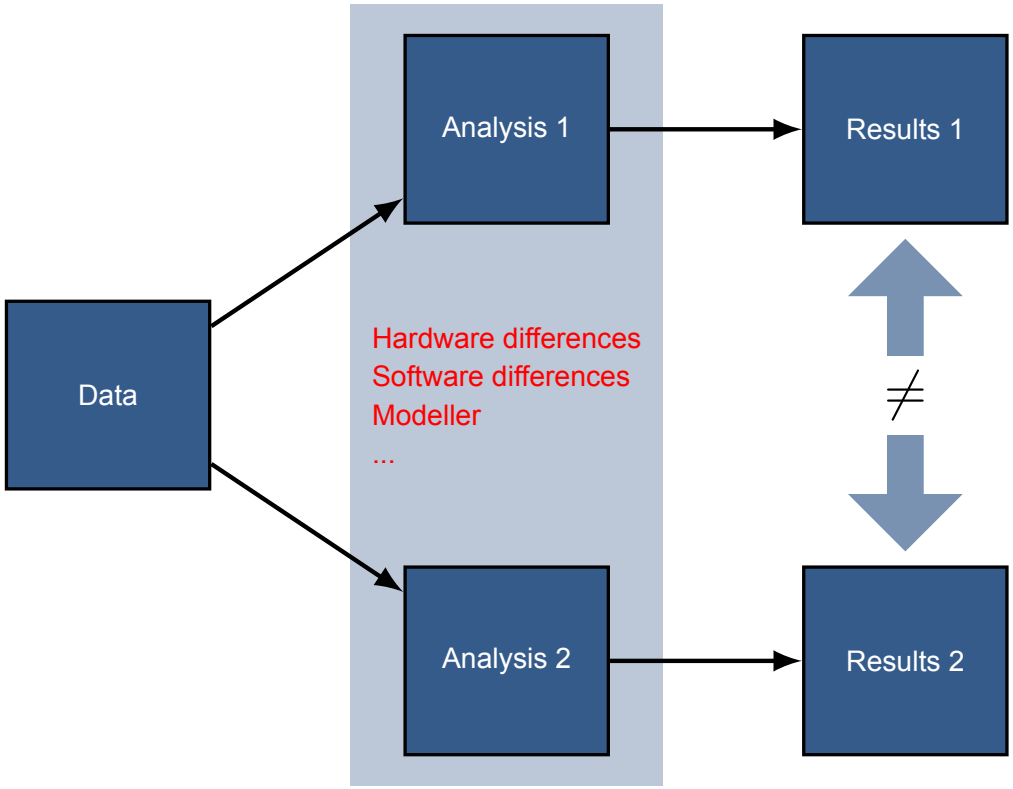

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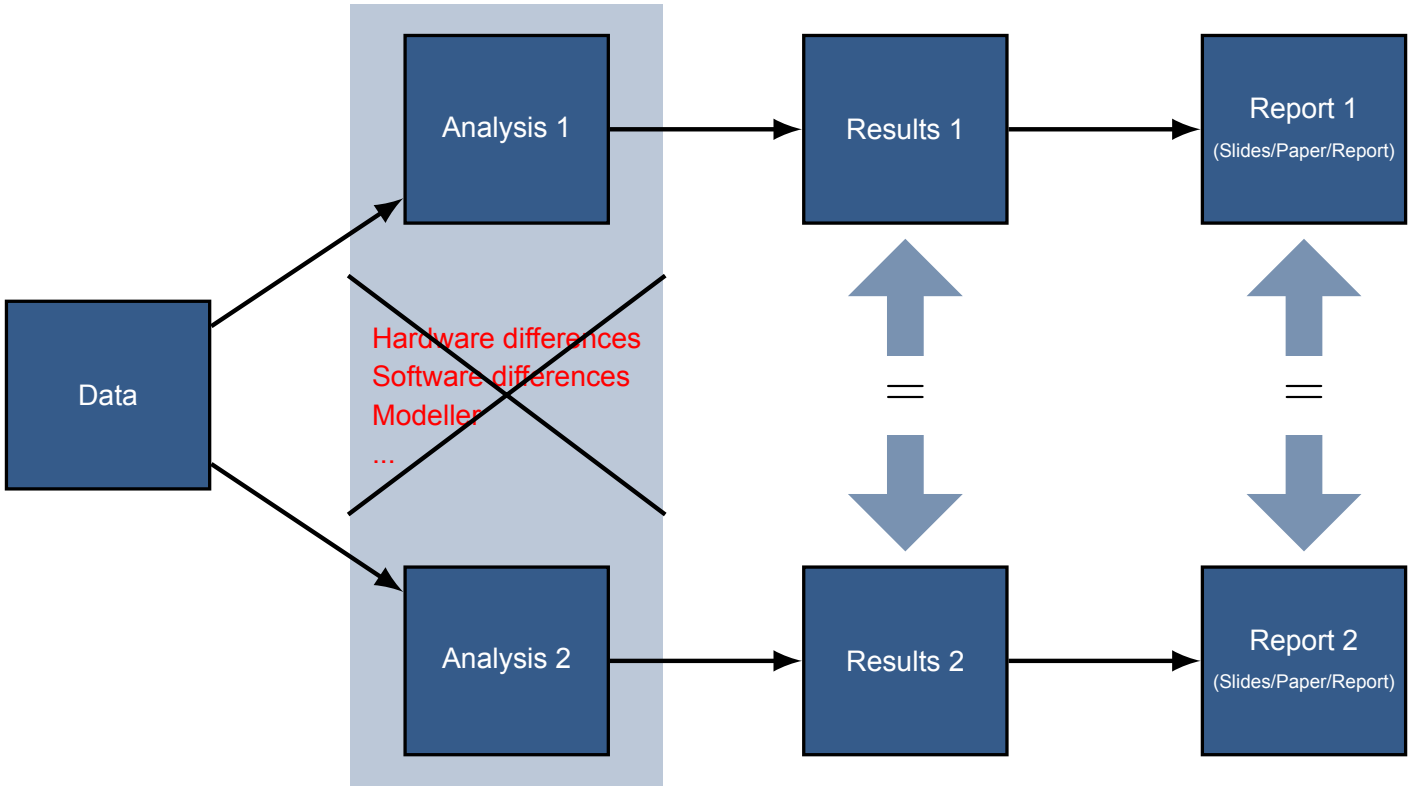

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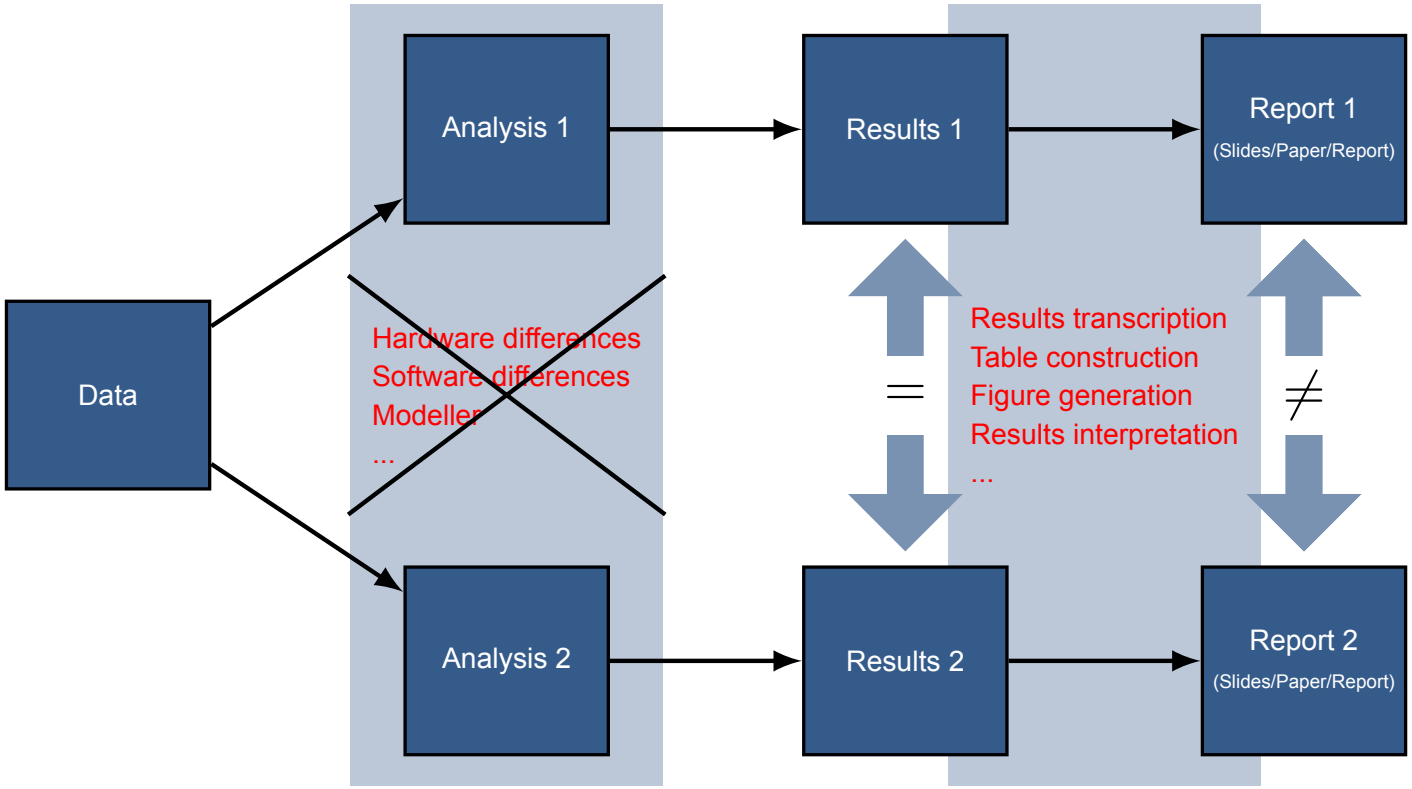

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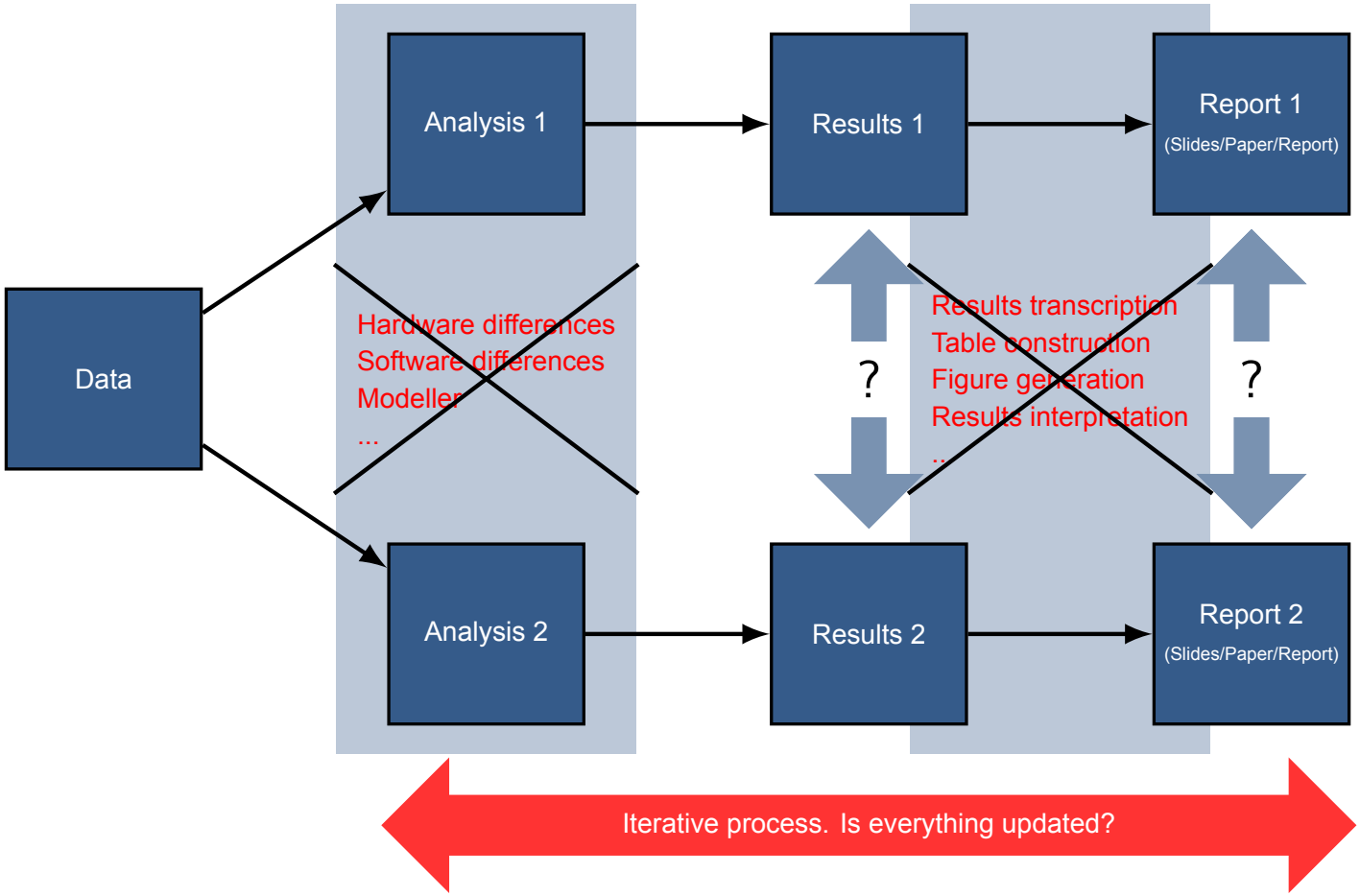

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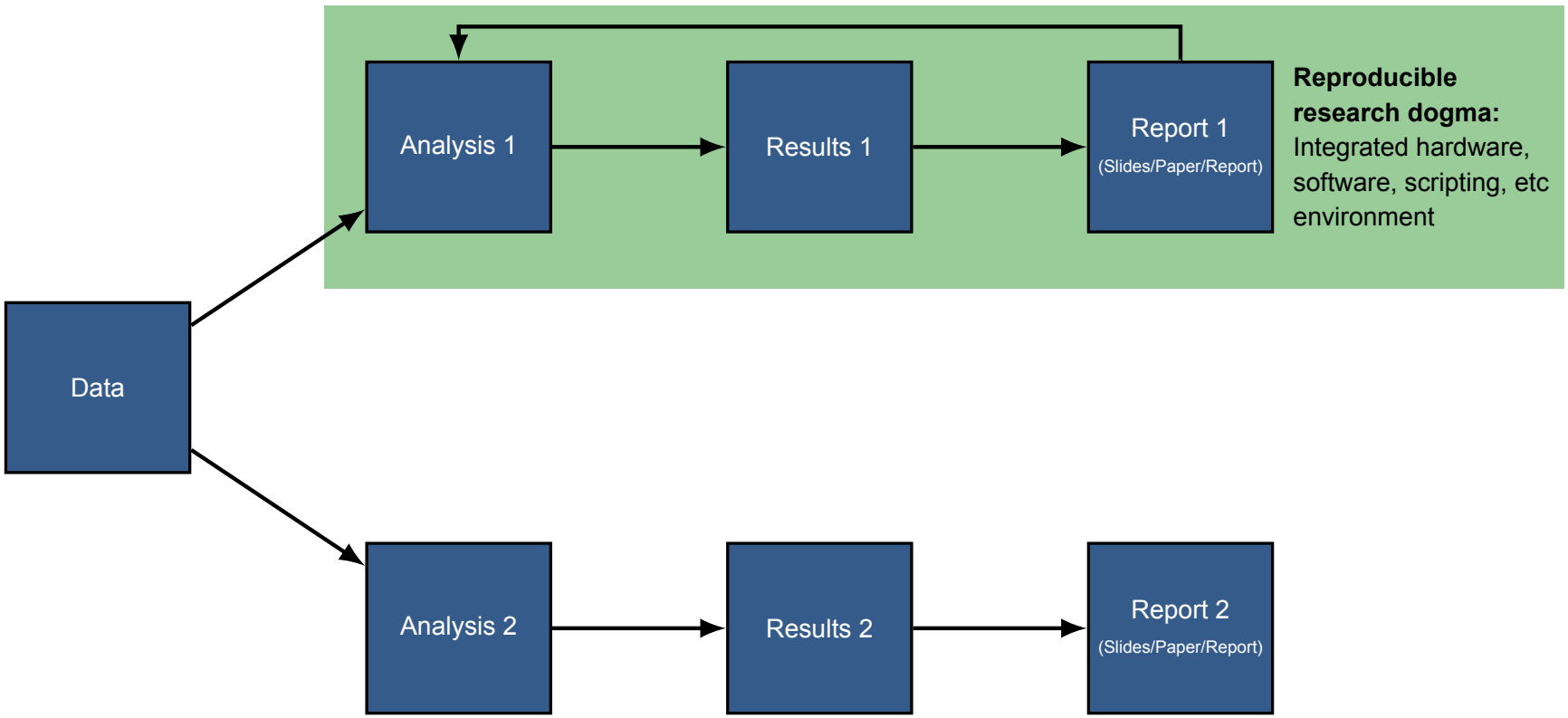

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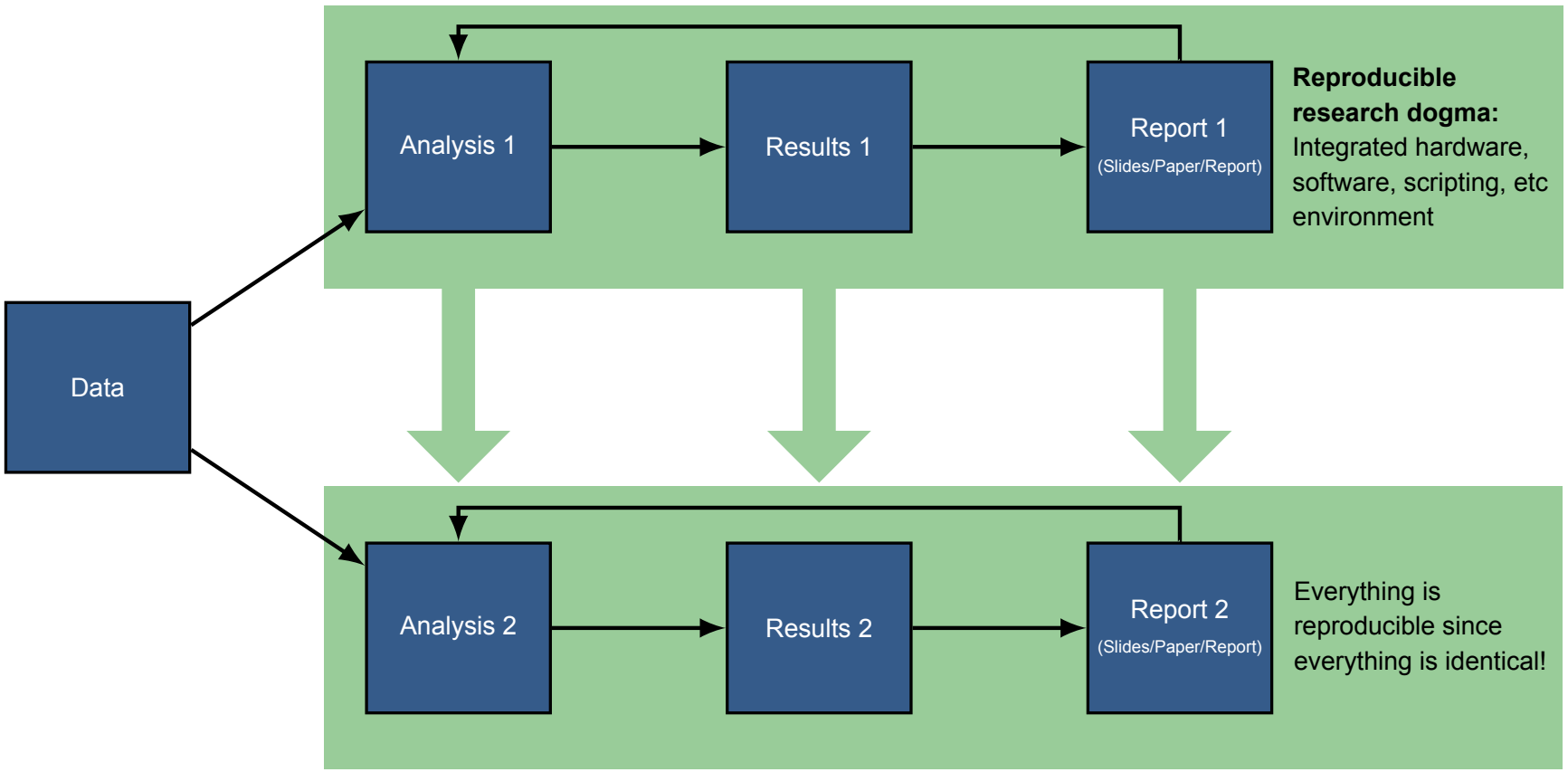

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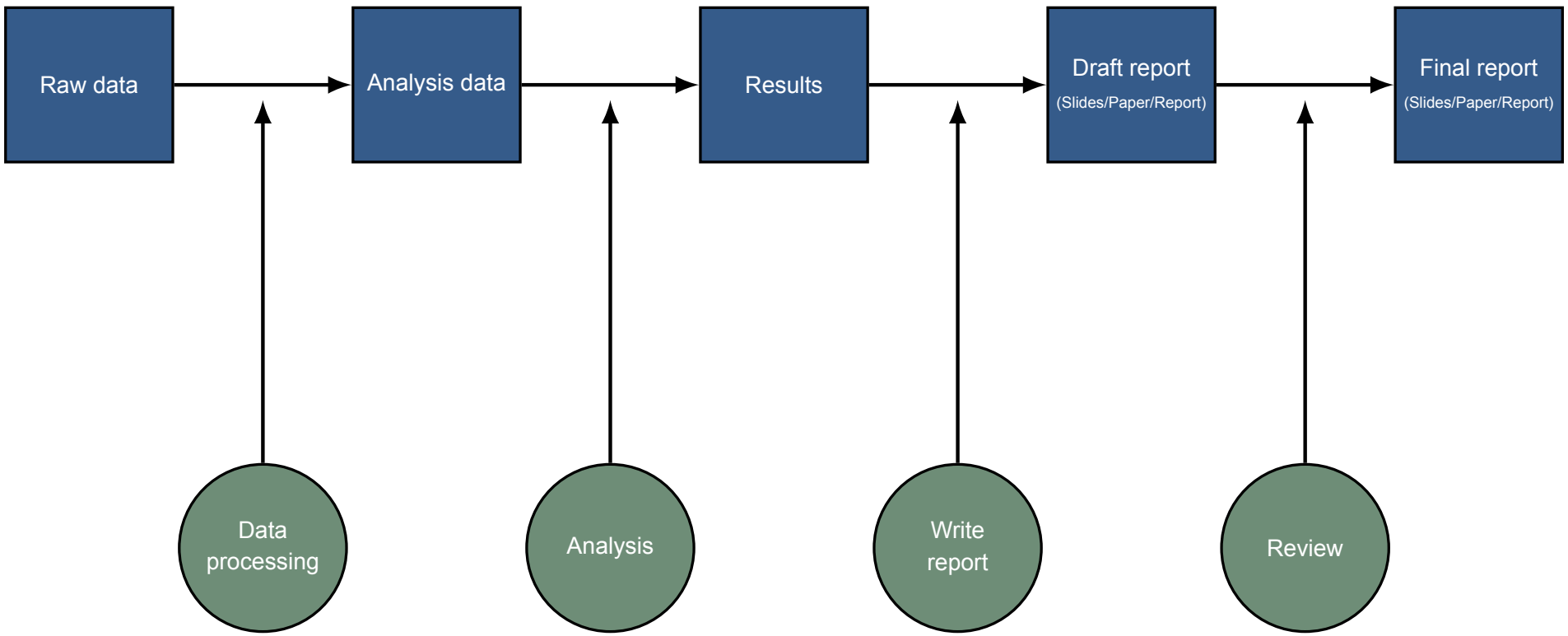

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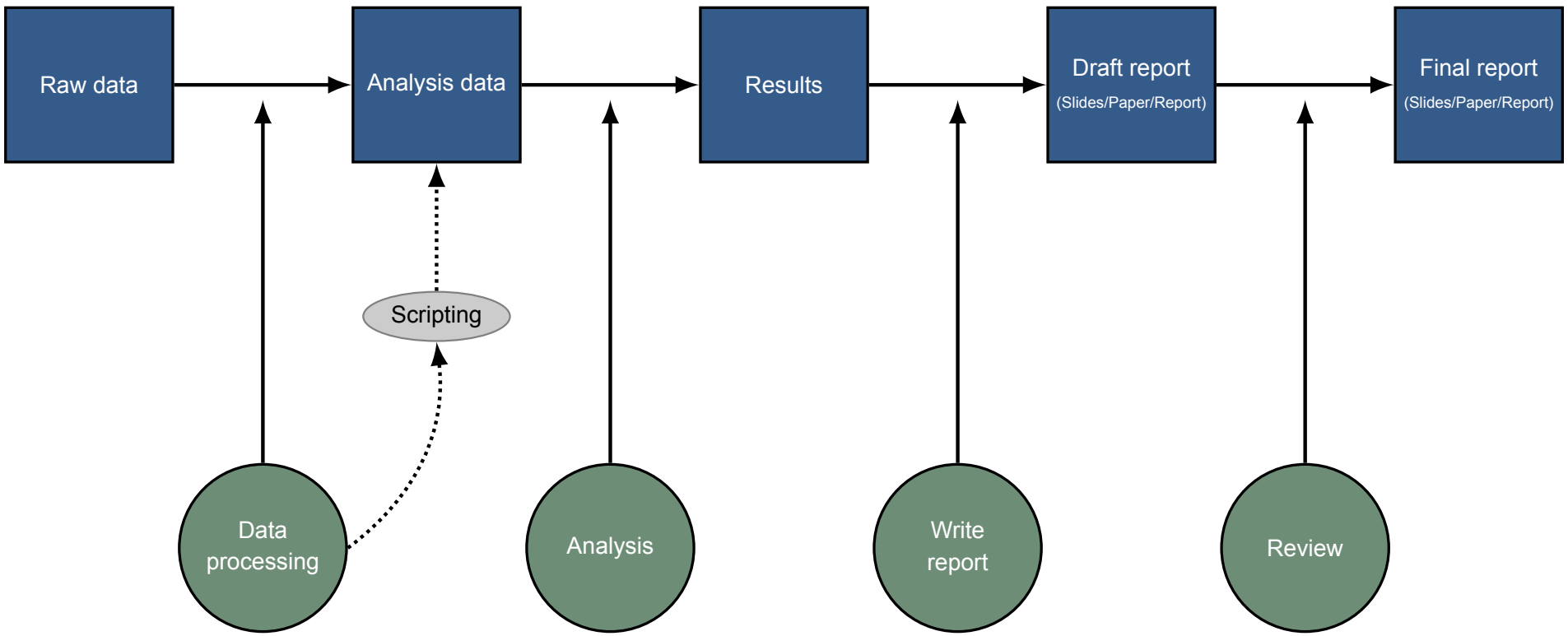

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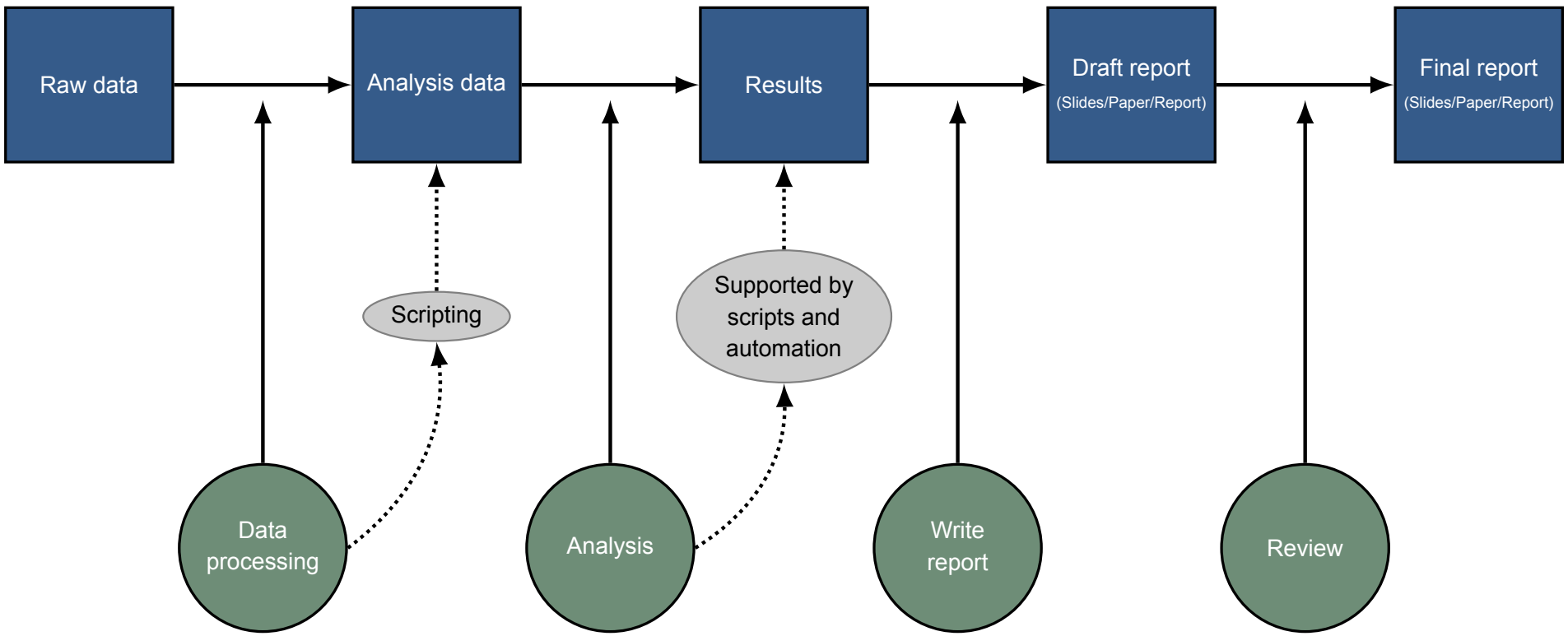

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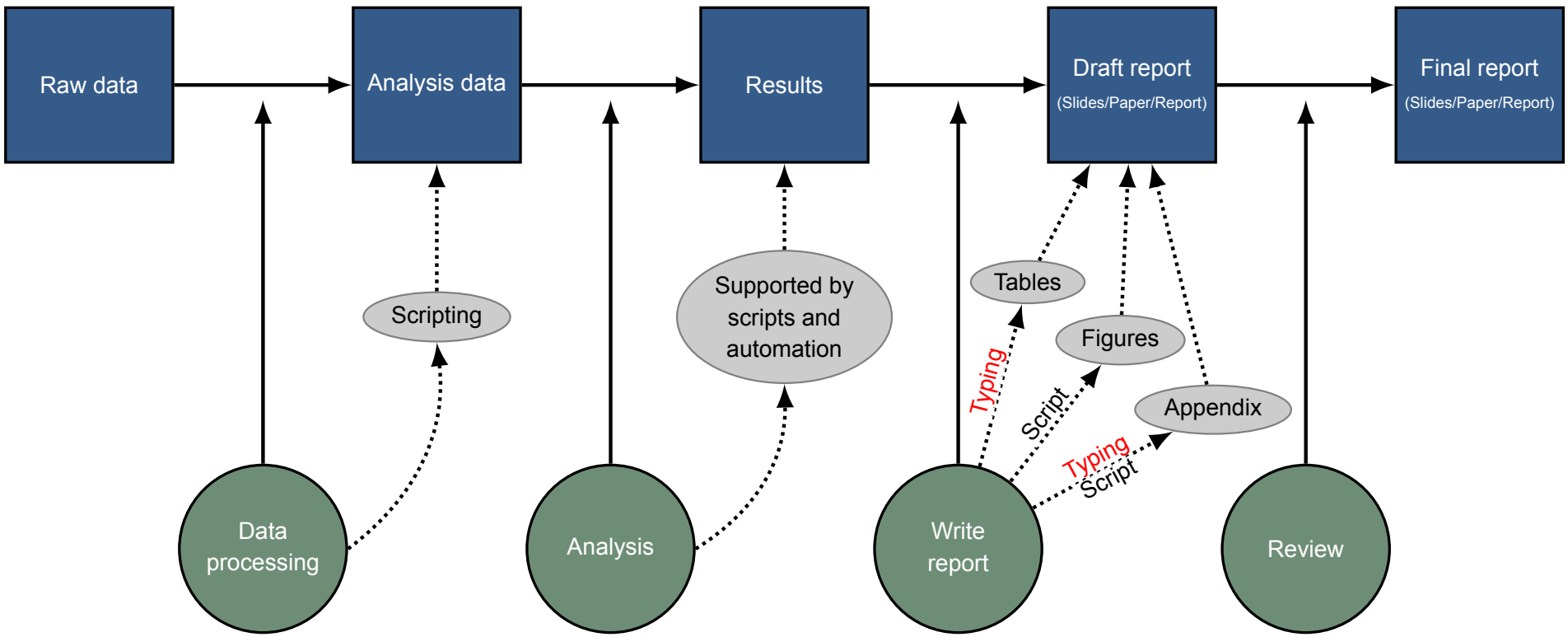

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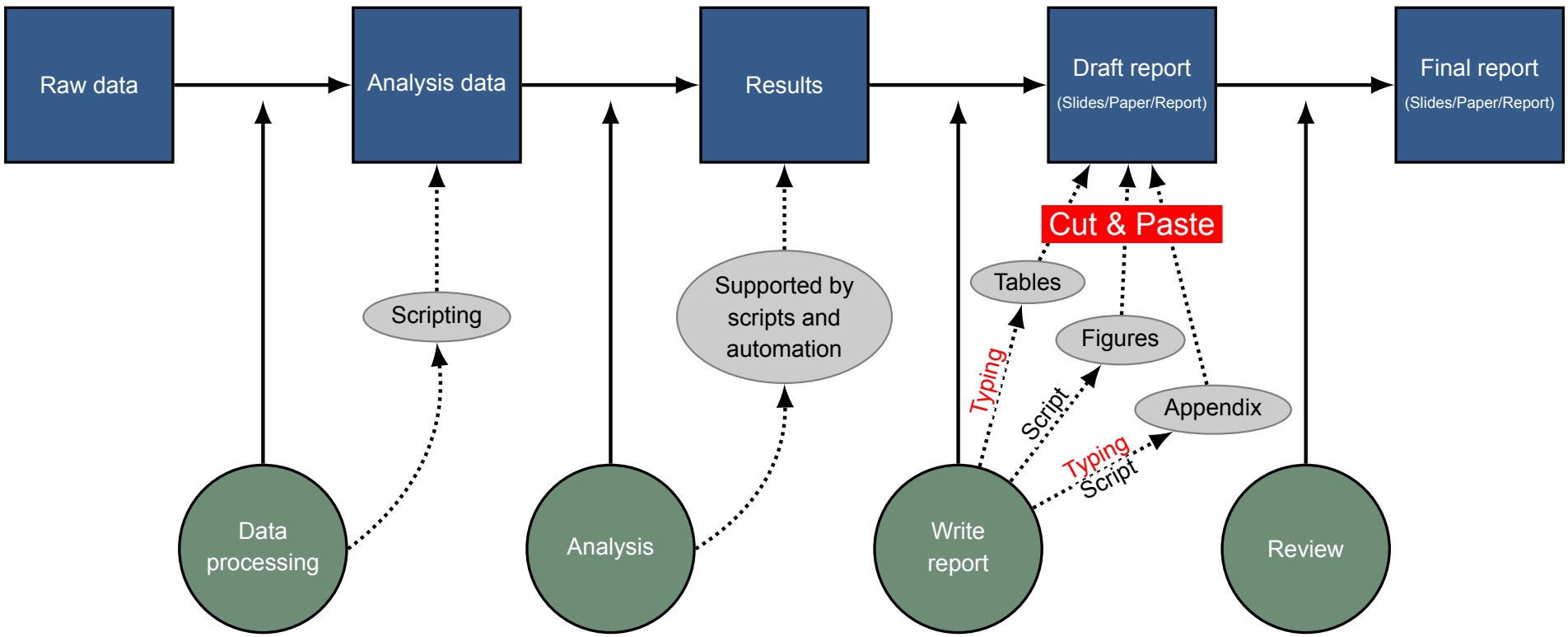

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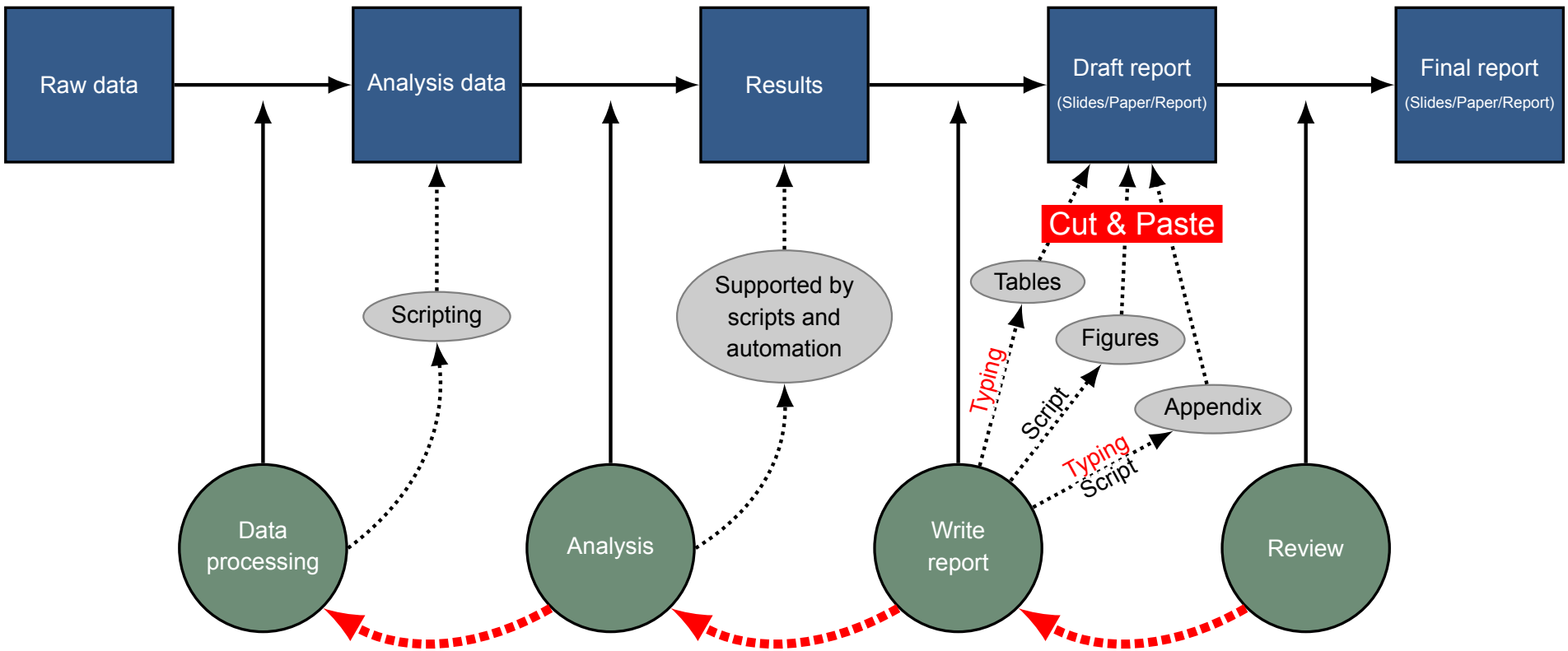

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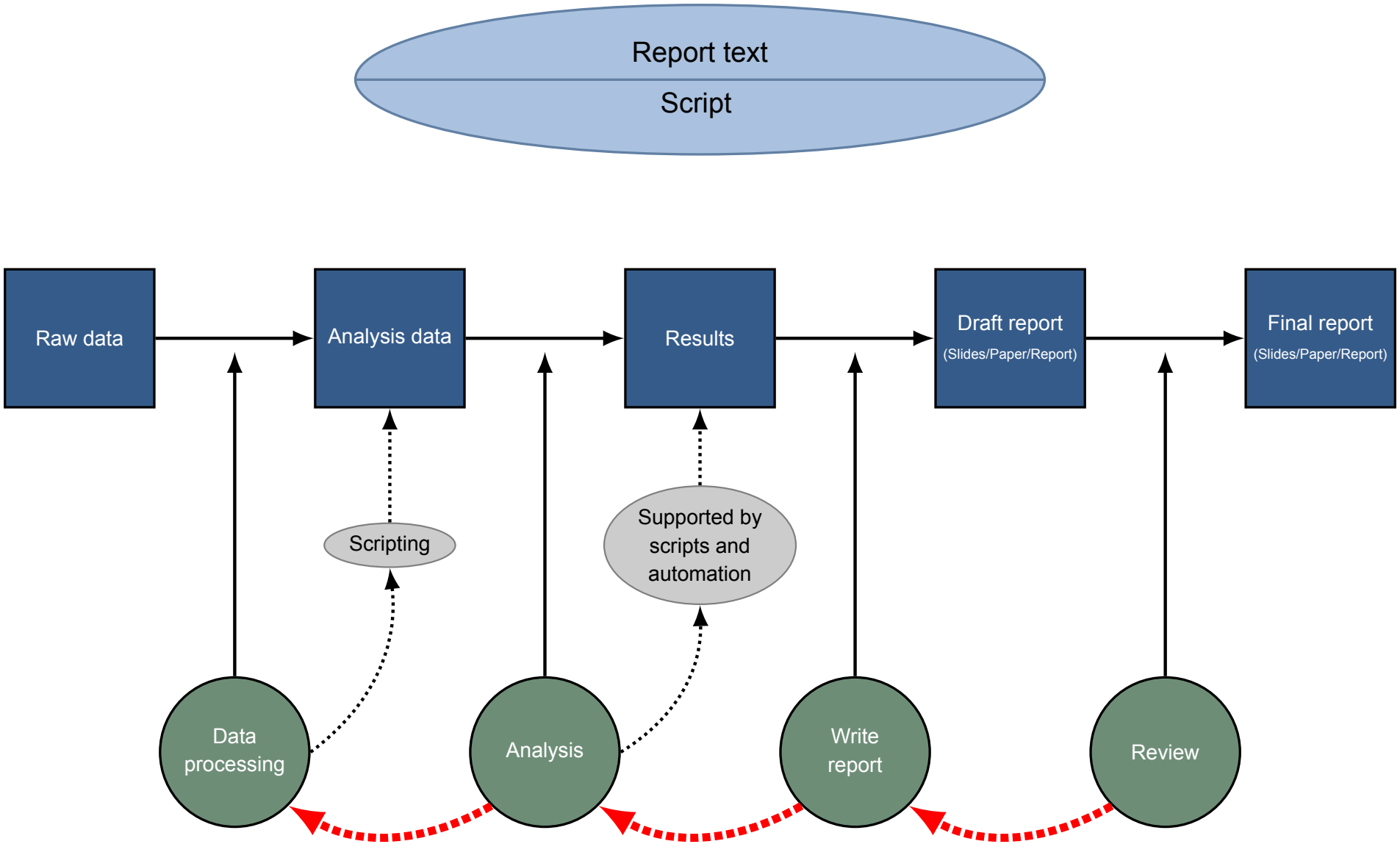

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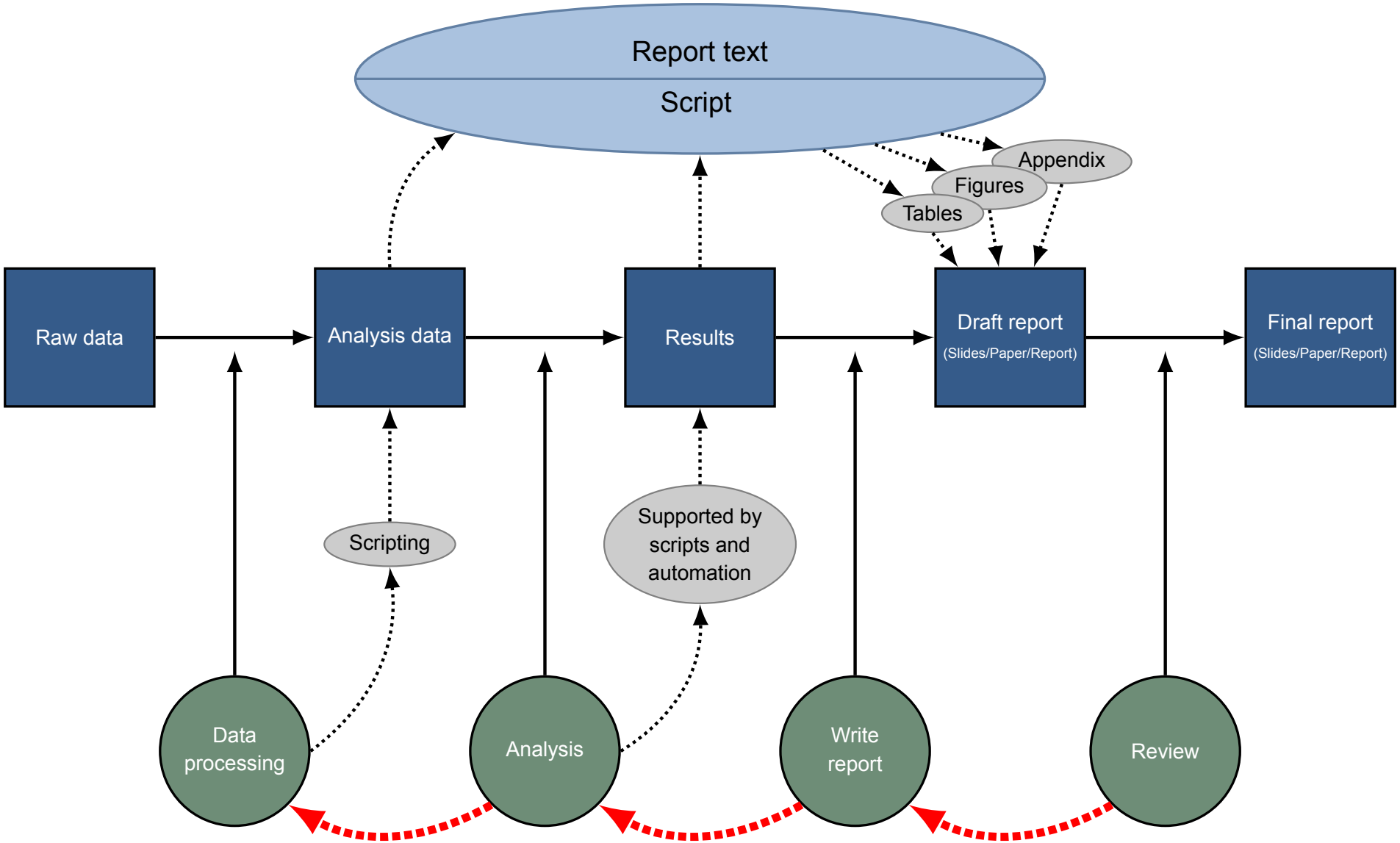

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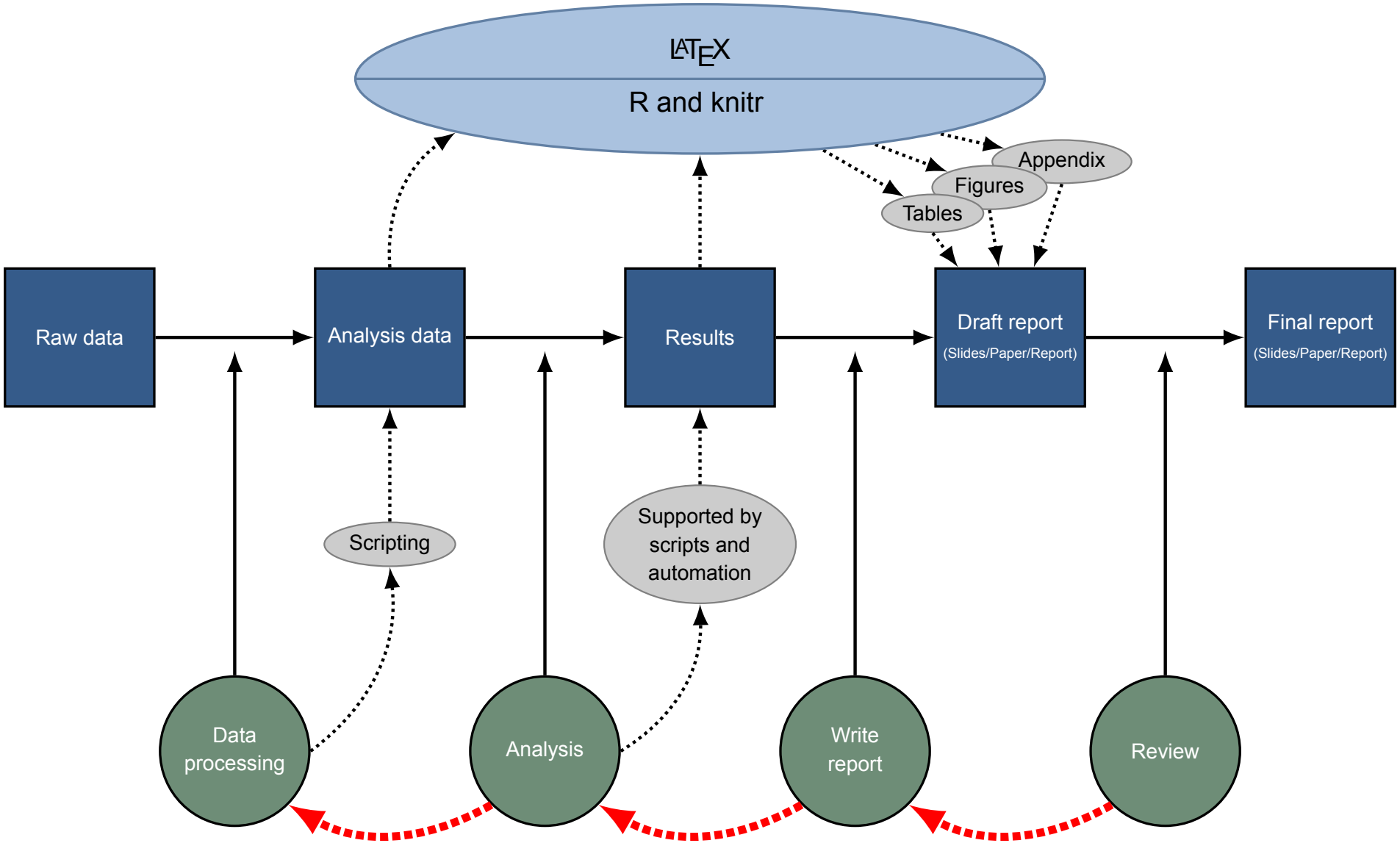

# Software for Reproducible Research

- Proprietary / in house / platform or IT environment-specific software
  - Track record varies
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  - Difficult to establish a common standard
- LaTeX+ R + RStudio + knitr
  - Open source - available to everyone at no cost.
  - Not specific to pharmacometrics - leverages developments in other fields.
  - RStudio offers an integrated analysis and document preparation environment.

# **LaTeX** is a markup language

A LaTeX file (left) is plain text. After submitting it to LaTeX (`latex latexfile.tex`) the result is a PDF file (right).

```
\documentclass[a4paper]{article}
\usepackage{graphicx}

\title{Example of \LaTeX}
\author{E Niclas Jonsson \and Justin J Wilkins}


\begin{document}

\maketitle


\section{Introduction}

Add some text of introduction.


\section{Methods}

Some methods.

\section{Results}

The results can be seen in Figure~\ref{fig:results}.

\begin{figure}

\includegraphics{myPlot}

\caption{This is the caption.} \label{fig:results}
\end{figure}

\end{document}
```

Example of LaTeX

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June 9, 2013

## 1 Introduction

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The results can be seen in Figure 1.

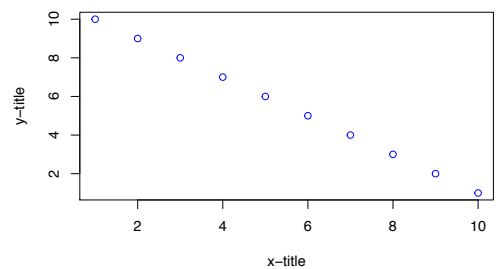


Figure 1: This is the caption.

1

# With **knitr**, it is possible to mix LaTeX and R code

The file is first sent to `knitr` in R, which generates a LaTeX file, which in turn is sent to LaTeX to generate the PDF.

```
\documentclass[a4paper]{article}
\usepackage{graphicx}

\title{Example of knitr and \LaTeX}
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\begin{figure}
<<myPlot,fig.width=6,fig.height=4>>=
plot(1:10,10:1,col="blue",xlab="x-title",ylab="y-title")
@
\caption{This is the caption.} \label{fig:results}
\end{figure}

\end{document}
```

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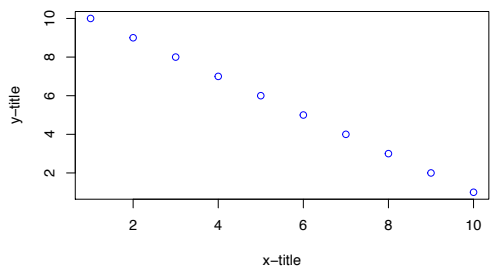


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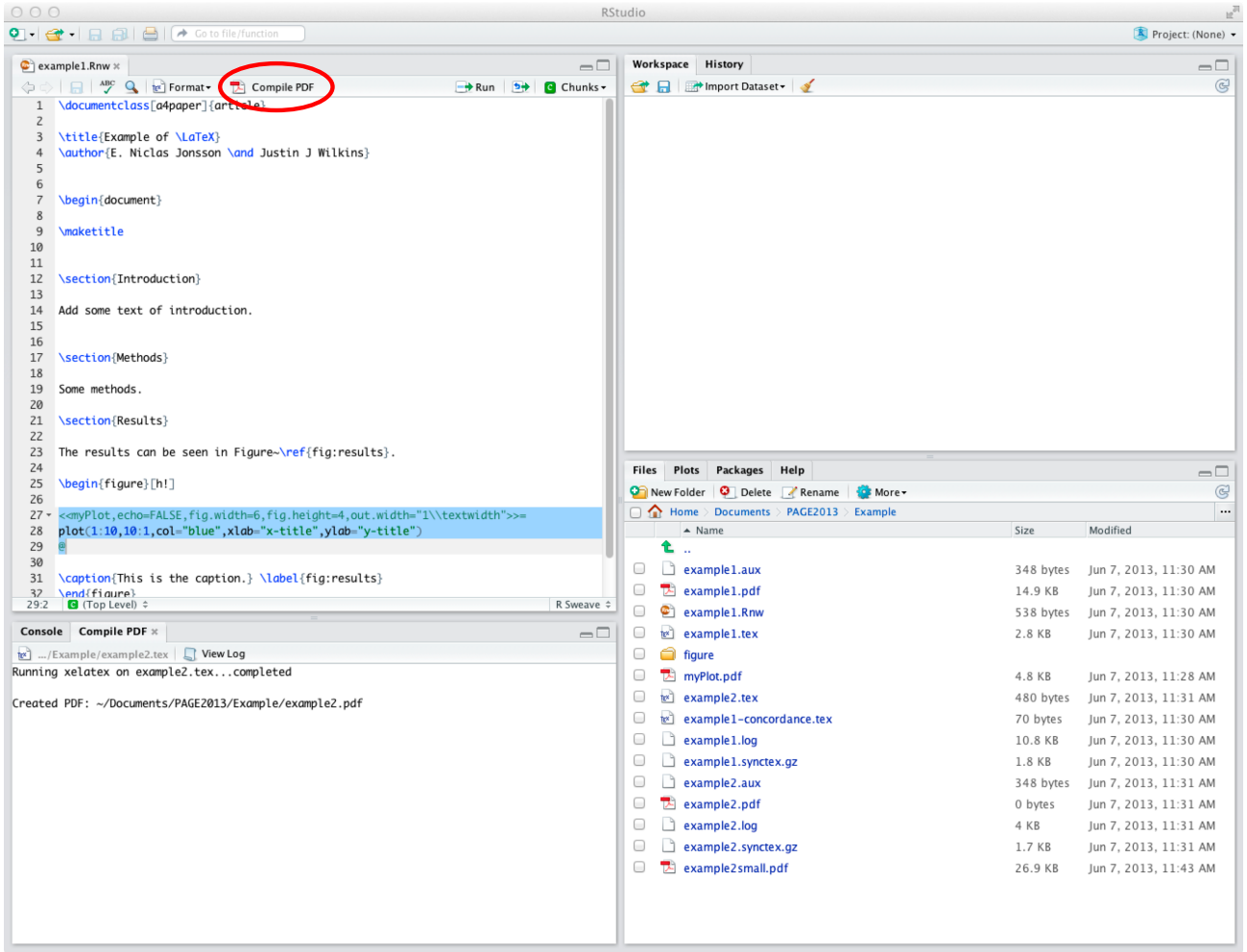
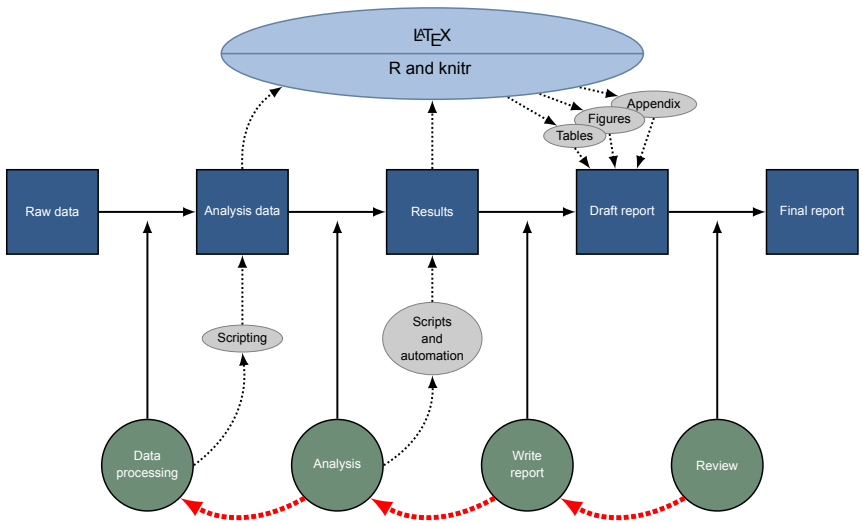
**RStudio** brings R, knitr and LaTeX together in a clean, integrated environment, with document generation at the push of a button



# Benefits of a Reproducible Research workflow in pharmacometrics

- Reproducibility(!)
- Documentation
- Efficiency
- Very template oriented
- Possibility to prepare reports before final data and models
- Very good for large complicated technical documents



# Drawbacks with LaTeX and knitr

- Steep learning curve
- Very template oriented
- Integration into existing IT environments
- Unfamiliar and archaic interface...

# A bit like this really

```
$PROB  THEOPHYLLINE   POPULATION DATA
$INPUT      ID DOSE=AMT TIME CP=DV WT
$DATA       THEOPP

$SUBROUTINES  ADVAN2

$PK
;THETA(1)=MEAN ABSORPTION RATE CONSTANT (1/HR)
;THETA(2)=MEAN ELIMINATION RATE CONSTANT (1/HR)
;THETA(3)=SLOPE OF CLEARANCE VS WEIGHT RELATIONSHIP
;SCALING PARAMETER=VOLUME/WT SINCE DOSE IS WEIGHT-ADJUSTED
   CALLFL=1
   KA=THETA(1)+ETA(1)
   K=THETA(2)+ETA(2)
   CL=THETA(3)*WT+ETA(3)
   SC=CL/K/WT

$THETA  (.1,3,5) (.008,.08,.5) (.004,.04,.9)
$OMEGA BLOCK(3)  6 .005 .0002 .3 .006 .4

$ERROR
   Y=F+EPS(1)

$SIGMA  .4

$EST     MAXEVAL=450  PRINT=5
$COV
$TABLE          ID DOSE WT TIME
$SCAT           (RES WRES) VS TIME BY ID
```

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# The end product is a PDF file

- No ”standard” Office document is involved in the report generation process.
- In many organizations the final report version is a PDF.
- PDFs can (almost) be converted to Microsoft Word
  - Possibly useful for the review process...
  - Not for the final document since it *breaks the traceability chain*!

And now, a live demonstration!

Because we know you won't believe us when we tell you it's easy.

# Conclusions

Reproducible Research methodology:

- improves consistency and efficiency of pharmacometric analyses and report generation.
- is not particularly difficult to implement.
- enhances both technical and scientific quality.

Come visit us in our booth!