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世界中医药学会联合会

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# 网络药理学评价方法指南

# Network Pharmacology Evaluation Methodology Guidance



世界中联国际组织标准

International Standard of WFCMS

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# 前　言

主要起草单位：清华大学、世界中医药学会联合会网络药理学专业委员会

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本文件起草程序遵守了世界中医药学会联合会发布的《世界中联国际组织标准管理办法》和 SCM 0001-2009《标准制定和发布工作规范》。

# 引　言

网络药理学是人工智能和大数据时代药物系统性研究的新兴、交叉、前沿学科，强调从系统层次和生物网络的整体角度出发，解析药物及治疗对象之间的分子关联规律，其主要研究内容是药物研究，尤其为中药复杂体系研究提供了新思路，被广泛应用于药物和中药活性化合物发现、整体作用机制阐释、药物组合和方剂配伍规律解析等方面，为临床合理用药、新药研发等提供了新的科技支撑。

在大数据背景下，随着网络药理学的影响力和应用日益广泛，网络药理学在理论分析、算法发展和实际应用等方面，面临着重要的发展机遇和挑战。如何整合临床病案、实验的海量数据，结合科学验证，揭示网络药理学调控机制，从而更有效地开展网络药理学研究，成为研究者们关注的核心问题。同时，目前网络药理学研究存在质量良莠不齐、数据缺乏规范、科学检验不足等问题，亟须建立严谨规范、科学统一的网络药理学研究评价标准，以保障该新兴学科的健康发展。

本文件以网络药理学的核心理论“网络靶标”为基础，建立药物与疾病在生物分子网络上的关联机制，形成“网络靶标-系统调节”研究模式和方法体系，为理解和解释药物与生物系统之间的相互作用找到一种新的思路与方法。

本文件通过建立网络药理学评价规范性标准，推动基于“网络靶标-系统调节”的研发模式成为更严谨、更科学，以及被更广泛认可的新一代药物研究范式，推动网络药理学更规范地应用于药物分析和实验、临床药理学研究中，促进该学科快速、健康与有序发展。

由于网络药理学研究的多样性、复杂性，以及目前研究水平与条件的局限性，其评价方法和内容尚有诸多问题亟待进一步解决，本文件将结合网络药理学研究以及学科发展不断修订和完善。

# 网络药理学评价方法指南

## 1 适用范围

本文件规定了网络药理学研究过程中数据收集、网络分析，以及实验验证的原则、流程和评价指标等。

本文件适用于从事网络药理学及相关学科的研究人员。

本文件适用于植物药、动物药、化学药、生物药等药物作用分析，以及疾病机制分析。

## 2 规范性引用文件

下列文件对于本文件的应用是必不可少的。凡是注日期的引用文件，仅注日期的版本适用于本文件；不注日期的引用文件，其最新版本（包括所有的修改单）适用于本文件。

GB/T 36344-2018 信息技术 数据质量评价指标

GB/T 34945-2017 信息技术 数据溯源描述模型

AIOSS-01-2018 人工智能 深度学习算法评估规范

## 3 术语和定义

下列术语和定义适用于本文件。

3.1

**网络药理学**

融合系统生物学、生物信息学、网络科学等学科，从系统层次和生物网络的整体角度出发，解析药物与治疗对象之间的分子关联，揭示药物的系统性药理机制，从而指导新药研发和临床诊疗，是人工智能和大数据时代药物系统性研究的新兴原创科学。

3.2

**网络靶标**

生物分子网络中，能够机制性关联药物与疾病，并定量表示药物整体调节作用机理的网络关键环节，包括关键分子、关键通路或关键模块等。

3.3

**物质基础**

现代药物或天然药物所含化学成分及其相关属性，包括化学物质的名称、类型、理化属性、药代动力学参数等。

3.4

**药物靶标**

体内能被药物作用的生物分子，包含蛋白质（Protein）、核糖核酸（RNA）、脱氧核糖核酸（DNA）等。

3.5

**网络分析**

针对疾病相关或药物干预的生物分子网络进行深度分析和挖掘，包括网络基本分析（度、介数、聚集系数等网络基本参数）和网络深度分析（网络模块、网络动态分析等）。

3.6

**生物功能注释**

针对疾病相关或药物干预的生物分子网络，应用生物信息学方法，进行生物通路（Pathway）、基因本体（GO）等功能注释与富集。

3.7

**生物功能预测**

基于网络分析的规律性结果，应用生物信息、人工智能等进行功能预测。

## 4 评价要求

网络药理学的评价要求分为一般性评价和扩展性评价两种形式：

a)一般性评价要求应满足网络药理学分析所必需开展的基本评价内容，是保证网络药理学分析结果真实可信的基本要求。

b)扩展性评价要求在一般性评价要求基础上，根据不同的分析对象（疾病、药物）和分析目的（数据库开发、算法开发、机制研究、诊疗发现、药物研发等），开展更加深入的评价分析（如表 1 所示）。

**表 1 评价要求**

| 评价内容 | | 面向疾病分析 | | | | 面向药物分析 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 数据库开发 | 算法开发 | 机制研究 | 诊疗发现 | 数据库开发 | 算法开发 | 机制研究 | 药物研发 |
| 可靠性 | 数据来源 | ● | ● | ● | ● | ● | ● | ● | ● |
| | 数据信息 | ● | ● | ● | ● | ● | ● | ● | ● |
| | 关联信息 | ● | ● | ● | ● | ● | ● | ● | ● |
| | 软件算法 | ○ | ● | ○ | ○ | ○ | ● | ○ | ○ |
| | 分析方法 | ● | ● | ● | ● | ● | ● | ● | ● |
| | 验证方法[1] | - | ● | ● | ● | - | ● | ● | ● |
| | 模型构建[2] | - | ○ | ● | ○ | - | ○ | ● | ○ |
| 规范性 | 信息提取 | ● | - | - | - | ● | - | - | - |
| | 信息转换 | ● | - | ○ | ○ | ● | - | ○ | ○ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 算法实现 | - | ● | - | - | - | ● | - | - |
| | 分析路径 | - | ● | ● | ● | - | ● | ● | ● |
| | 验证流程 | - | ● | ● | ● | - | ● | ● | ● |
| 合理性 | 数据筛选 | - | - | - | - | - | - | ● | ● |
| | 分析指标 | - | ● | ● | ● | - | ● | ● | ● |
| | 验证模型[2] | - | ○ | ● | ○ | - | ○ | ● | ○ |
| | 检测指标 | - | ● | ● | ● | - | ● | ● | ● |
| 注：“●”一般性评价内容；“○”扩展性评价内容；“-”不作要求。<br>注 1：验证方法主要包含临床、实验等方法。<br>注 2：模型构建与验证模型中的“模型”主要是指动物、细胞等模型。 | | | | | | | | | |

## 5 评价过程

评价过程包括数据收集、网络分析和结果验证。针对每个评价过程，主要从可靠性、规范性与合理性三个方面进行具体评价（如表 2 所示）。

表 2 评价过程

| 评价内容 | 评价过程 | | |
|---|---|---|---|
| | 数据收集 | 网络分析 | 结果验证 |
| 可靠性 | 数据来源<br>数据信息[1]<br>关联信息[2] | 软件算法<br>分析方法 | 验证方法<br>模型构建 |
| 规范性 | 信息提取<br>信息转换 | 算法实现<br>分析路径 | 验证流程 |
| 合理性 | 数据溯源<br>数据筛选 | 分析指标 | 验证模型<br>检测指标 |
| 注 1：数据信息包括疾病、疾病靶标、药物、药物成分、成分靶标等。<br>注 2：关联信息包括蛋白质相互作用、基因与蛋白质对应关系、蛋白质与代谢物相互作用、代谢物反应过程等。 | | | |

## 6 评价内容

### 6.1 可靠性评价

评估网络药理学分析中主要数据及其关联信息的获取、软件算法与分析方法的设计以及验证方法的选择与模型构建，是否可靠、能否满足分析要求。根据网络药理学分析的一般流程，可划分为数据收集、网络分析和结果验证三个不同的过程，针对不同过程进行相应的可靠性评价，评价要素与评价指标的选择可参考表 A.1 所示。

#### 6.1.1 数据收集

主要评价药物的物质基础、生物靶标等基础数据来源及收集方法的可靠性。数据收集主要包括文献查询、软件预测、数据库检索、实验数据分析等。本指南优先推荐采用经严谨实验验证或权威文献来源的数据，对于软件预测和非文献来源的数据库数据，应尽量提供数据的可信度评价，推荐采用高信度的数据。

6.1.2 网络分析

评价生物靶标网络分析中新开发算法的可靠性，或拟选择分析方法的正确性与稳定性。

针对新开发的算法常用的评价指标包括算法实现、功能的正确性，以及算法性能的准确率、召回率和 F 值等。

针对将相关领域已成熟的分析方法应用于网络药理学分析，推荐采用标准数据集或实验数据对拟选用的方法进行可靠性分析，其中标准数据集应参考数据收集进行可靠性评价。

针对应用已有的网络药理学分析方法，应明确标注该分析方法的出处。

6.1.3 结果验证

主要评价采用方法的可靠性、可重复性等，保证验证结果和最终结论的可信度。评价对象包括但不限于评价方法的选择（计算机模拟、体内外实验及临床试验等）、评价模型的选择（蛋白晶体结构、细胞模型、动物模型等）、终点指标的选择（金指标、代表性指标等）等，本指南优先推荐采用体、内外实验或临床试验进行验证。

6.2 规范性评价

评价数据信息的提取与转换、软件/算法的开发、网络的构建与分析以及实验验证等流程是否规范，相关技术方法的应用是否准确，用于保障分析结果的准确性和可重现性，评价要素与评价指标可参考表 A.2 所示。

6.2.1 数据收集

评价数据收集过程中数据信息的完整性和可溯源性、数据提取的明确性以及数据处理的规范性。

6.2.2 网络分析

评价分析流程的明确性、方法评价的规范性以及分析方法的可溯源性。

6.2.3 结果验证

评价操作流程和结果分析的规范性。

6.3 合理性评价

评估数据筛选和过滤、网络分析指标的选择与阈值的确定、验证模型及检测指标的选择等内容的合理性，评价要素与评价指标可参考表 A. 3 所示。

6.3.1 数据收集

评价数据收集过程中关键词选择、数据筛选原则等内容的合理性。

针对药效成分的筛选，应充分考虑分析对象、吸收途径、药效部位、显效成分、代谢形式、生物利用度、成药性等影响药效学行为因素，选取影响药效学行为的参数进行药效成分筛选。

针对靶标或靶标间相互作用等信息的筛选，应着重考察数据的可信度及获取方法合理性等因素。

### 6.3.2 网络分析

评价用于筛选重要作用靶标（群）、关键药效成分（群）等要素的网络分析指标的合理性。网络分析相关指标包括：节点与边的特征（如节点度、节点中心性、边权重等）、网络的凝聚性（如密度、聚类系数、子图、连通性等）、网络的可分割性（如层次聚类、谱分割等）、网络模块性、网络基序等。

针对研究的具体疾病，应该综合考虑以上指标，建立合理的病证生物分子网络，确定适宜的网络靶标。

如使用全新计算方法确定药效成分群及网络靶标，还应该考察所选药效成分及网络靶标对整体网络稳态的重要性。

### 6.3.3 结果验证

评价临床试验设计的合理性、模型的代表性与适用性、检测指标与网络分析结果的相关性等因素。

对于新开发的网络药理学分析算法，需根据结果类型提供适宜的性能评价指标，对其预测结果进行验证，必要时可采用标准数据集进行验证。

# 附录 A
（资料性附录）
# 评价要素与评价指标

## A.1 可靠性评价要素与评价指标

可靠性评价要素与评价指标可参考表 A.1。

表 A.1 可靠性评价要素与评价指标

| 评价过程 | 评价要素 | 评价指标 |
|---|---|---|
| 数据收集 | 数据的准确性 | 准确率、查准率 |
| | 数据的完整性 | 查全率 |
| | 数据的可获取性 | 是否公开可获取 |
| 网络分析 | 算法的正确性 | 算法功能的正确性、算法实现的正确性 |
| | 算法的准确性 | 准确度、特异性、灵敏度、召回率、F 值 |
| | 分析的稳定性 | 均方根误差、平均绝对误差 |
| 结果验证 | 方法的可靠性 | 信度[1]、效度[1] |
| | 结果的可重复性 | 一致率 |
| 注 1:信度、效度主要适用于采用临床研究、动物或细胞模型等进行验证的可靠性评价。 | | |

## A.2 规范性评价要素及评价指标

规范性评价要素及评价指标可参考表 A.2。

表 A.2 规范性评价要素及评价指标

| 评价过程 | 评价要素 | 评价指标 |
|---|---|---|
| 数据收集 | 数据描述的完整性 | 数据内容的关键信息是否描述清楚 |
| | 数据的可溯源性 | 依据描述信息能否溯源相关数据 |
| | 数据提取的明确性 | 关键词描述是否确切<br>提取规则和方式是否清晰 |
| | 数据处理的规范性 | 不同来源数据转换、对接方法的描述是否明确 |
| 网络分析 | 分析流程的明确性 | 算法设计或网络分析的流程是否描述清楚 |
| | 方法评价的规范性 | 算法开发是否进行严谨的方法学评价 |
| | 分析方法的可溯源性 | 应用的分析方法或技术指标是否能够溯源 |
| 结果验证 | 操作流程的规范性 | 采用的模型是否明确<br>操作流程的描述是否清楚 |
| | 结果分析的规范性 | 结果的评价指标是否明确<br>结果的描述是否客观、准确 |

## A.3 合理性评价要素及评价指标

合理性评价要素及评价指标可参考表 A.3。

**表 A.3 合理性评价要素及评价指标**

| 评价过程 | 评价要素 | 评价指标 |
|---|---|---|
| 数据收集 | 信息提取的合理性 | 检索关键词的选择与研究目标是否相符；<br>检索关键词是否完备 |
| | 信息筛选的合理性 | 数据筛选原则是否符合研究内容的相关要求；<br>选择的筛选指标是否能达到筛选要求 |
| 网络分析 | 分析方法的适用性 | 采用的网络分析方法是否与研究目标相符合 |
| | 分析指标的合理性 | 选择的分析指标是否满足网络分析的需求 |
| 结果验证 | 模型的适用性 | 采用的模型与研究目标是否相关、是否具有代表性 |
| | 评价指标的合理性 | 评价指标是否符合研究目标要求 |

# 附录 B

## （资料性附录）
## 研究报告书写规范

### B1 题目和摘要

题目和摘要中均应标明研究对象，摘要中还应简述网络药理学分析的研究目的、研究方法、研究结果、研究结论及意义等。

### B2 前言

应详细阐述研究背景和原理等内容，针对具体的研究目标尽可能提供确切的临床疗效或试验证据，如高质量的 RCT 研究、队列研究、真实世界的研究成果，或可靠的研究数据等。

### B3 方法与结果

#### B3.1 研究设计

应报告研究设计的关键内容概况，如研究对象、研究方法、研究类型（干实验、干湿结合实验）、数据来源（获取数据的方法），必要时应提供研究流程图。

#### B3.2 研究对象

B3.2.1 面向疾病的研究，应提供疾病标准名称，必要时提供现行版 ICD 疾病编码号，中医证候研究应正确描述证候名称。证候名称应符合中医临床诊疗术语国家标准（证候部分）的相关要求。

B3.2.2 面向药物的研究，化合物应提供标准化合物名称或具有唯一标识的化合物信息，必要时提供结构式；中药复方应提供处方来源、组成以及每味药物的标准名称。中药外文名称推荐使用拉丁名或英文名。

#### B3.3 数据来源

B3.3.1 应尽可能详细描述数据的来源，如文献数据、数据库检索或实验数据等，对获得数据的方式应提供可重现的所有细节参数，必要时提供数据源的局限性描述。

B3.3.2 来源于数据库检索的数据应提供数据库名称、来源、版本号、检索日期、检索策略，web 数据库应该提供数据库参考文献，必要时应提供访问地址及数据收录情况等描述性统计；来源于文献的数据应提供原始参考文献，并描述原始文献数据获得的方法，必要时还应对文献数据进行描述性统计；来源于实验的数据应提供具体的实验方法、实验对象（与本研究对象的关系）、实验条件，以及实验结果获取方式，必要时还应提供实验方法的方法学验证结果。

#### B3.4 网络分析

B3.4.1 应详细描述构建网络的相关要素及其相互关系，以及网络分析的方法和指标，对网络分析结果应有生物学意义的阐述。其中，网络的构建应描述网络相关元素与整体数据的关系，如果是经过筛选的子集，应体现合理性，应提供具体的筛选方法、筛选依据、筛选原则，并阐述与研究目的的关系。

B3.4..2 网络分析的方法应具体描述如下内容：

——分析内容与指标，如网络的基本参数（节点与边的特征、网络的凝聚性特征、网络模块化特征）及这些参数与研究目的的关系；

——网络分析策略，必要时提供分析的路径流程图，对于非原创的网络分析方法应提供方法的来源、分析参数、参考文献、分析软件名称版本号，有参数选择的分析算法必要时应提供敏感性分析结果；

——原创性分析算法应描述新算法的原理、具体实施步骤、实现方式、参数设置、编程语言，如果使用标准数据集，应提供标准数据集的可靠性分析结果，必要时应提供与主流算法的比较结果及稳健性分析结果；

——网络分析结果要有明确的生物学意义，如有生物功能注释，应提供注释的类别（GO、Pathway、Disease 等），详细描述注释的方法、参数、软件名称及版本号，并详细阐述与研究目的的关系。

B3.5 **结果验证**

B3.5.1 应详细描述验证的方法、策略及与研究目的的关系，推荐联合多种方式进行验证，非原创方法不推荐仅使用计算机辅助或文献数据的方式进行验证。

B3.5.2 结果验证应提供的内容：

——计算机辅助验证应提供选择算法的名称、理由、出处、参考文献、参数设定、软件名称版本号及比较分析的结果；文献数据验证应提供选择依据、文献来源、检索日期，并描述源文献获取数据的方法及可靠性分析结果；

——实验研究验证应详细描述实验对象、实验材料、模型、实验方法、样本采集处理方法、检测指标、数据获取方式及分析结果，并阐明与研究目的的关系；

——临床研究验证应详细描述研究设计、研究对象、纳排标准、知情同意、试验实施流程、数据管理、样本采集策略及方法、样本处理方法、检测指标及统计分析结果，并阐明与研究目的的关系，必要时应提供伦理委员会审查批件。

B3.5.3 对于以开发网络药理学算法、数据库、计算分析平台等为主的研究，应对算法、数据库、平台等获得的预测分析结果进行合理且必要的验证：

——根据预测结果的类型提供分析的性能指标及可靠性评价指标，必要时应提供对标准数据集分析的一致性评价结果；

——通过实施严谨的临床试验或实验研究验证结果的可靠性。其中，基于临床、实验的可靠性验证拥有更高的证据等级。

B4 **讨论**

根据研究目标应谨慎给出总体的结果解释，在此基础上，方法学研究应增加对方法学可推广性的分析，应用类研究应增加对研究结果可解释性的分析。此外，还应对研究结果的局限性进行分析，包括不确定性的来源以及任何潜在影响研究结果的因素。

B5 **其他内容**

除上述报告内容外，原始数据还应明确是否可获得，必要时提供获取途径；分析方法应提供研究使用的软件包及其版本号清单，必要时提供分析算法源代码；未在文中展示的其他原始资料、方法及分析结果应提供获取补充信息的途径。

# Contents

# Foreword

**Main drafting organizations:** Tsinghua University, Specialty Committee of Network Pharmacology of World Federation of Chinese Medicine Societies (WFCMS).

**Drafting organizations participated:**

Institute of Chinese Medicine, Chinese Academy of Chinese Medical Sciences, The Fifth Medical Center of Chinese PLA General Hospital, Beijing University of Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Anhui University of Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Zhejiang Chinese Medical University, University of Macau, Shenyang Pharmaceutical University, Wenzhou Medical University, Zunyi Medical University, Lanzhou University, Beijing Jiaotong University, Tianjin International Joint Academy of Biomedicine, and Tsinghua-Fuzhou Data Technology Research Center.

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This document was drafted in accordance with the *WFCMS Regulations for International Organization Standard* and the *Working Regulation for Formulation and Publication of Standard* (SCM 0001-2009) both issued by WFCMS.

# Introduction

Network pharmacology is an interdisciplinary science newly developed in the systematic research of drugs based on artificial intelligence and the Big Data. It stresses the holistic system level and biological network when analyzing the molecular association laws between drugs and treatment objects. Focusing on studying drugs, it provides new ideas for especially the Chinese medicine research which has a complex system, and is widely applied to explore active compounds of drugs and Chinese medicine, explain the overall action mechanism, and analyze the compatibility regularity of drug pairs and formulas, etc. It has provided new science and technology supports for clinical rational use of drugs and drug development.

With an increasing influence and application in the Big Data era, network pharmacology is now facing with great development opportunities and challenges in terms of theoretical analysis, algorithm development and applications. The issue, how to integrate massive clinical and experimental data and combine the scientific verification to reveal the regulation mechanism of network pharmacology so as to carry out its research more effectively, has become the main concern of researchers. In addition, there are multiple problems in current network pharmacology studies, such as uneven research quality, lack of data standardization, and insufficient scientific verification. It is urgent to establish a rigorous, scientific and unified standard on evaluating network pharmacology studies to ensure the healthy development of this emerging discipline.

This document establishes the association mechanism between drugs and diseases in the biomolecular networks based on “network target”, the main theory of network pharmacology, and forms a “network target-system regulation” research mode and methodology, which provides a new idea and method for understanding and explaining the interactions between drugs and biological system.

By establishing the normative evaluation standard of network pharmacology, this document aims to make the "network target-system regulation" based research mode a new generation of drug research paradigm which is more rigorous and scientific and is widely recognized, and promote the standardized application of network pharmacology in drug analysis and experiment, and clinical pharmacological studies, thus promoting the rapid, healthy and orderly development of the discipline.

Due to the diversity and complexity of network pharmacology research, and limited by the current research level and conditions, there are still many problems in its evaluation method and content that need to be further resolved. Therefore, this document will be continuously revised following the development of network pharmacology research and the discipline.

# Guideline for Network Pharmacology Evaluation Methodology

## 1 Scope

This document specifies data collection and network analysis in the process of network pharmacology research, as well as experiment verification principles, procedures and evaluation indicators.

This document is applicable to the analysis on effects of botanical, animal, chemical and biological drugs, and disease mechanisms for researchers engaged in network pharmacology and related disciplines.

## 2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

GB/T 36344-2018 Information Technology—Evaluation Indicators for Data Quality

GB/T 34945-2017 Information Technology—Data Provenance Descriptive Model

AIOSS-01-2018 Artificial Intelligence—Assessment Specification for Deep Learning Algorithms

## 3. Terms and definitions

For the purpose of this document, the following terms and definitions apply.

**3.1**

**Network pharmacology**

It integrates systems biology, bioinformatics, network science and other disciplines, and analyzes the molecular relationship between drugs and

treatment objects to reveal the systematic pharmacological mechanism of drugs from an overall perspective of system level and biological network, thereby guiding the drug development and clinical diagnosis and treatment. It is a new original science of systematic drug research in the era of artificial intelligence and Big Data.

**3.2**

**Network targets**

The key network points in the biomolecular network that are mechanism-based associations between drugs and diseases, and that quantitatively indicate the overall regulation mechanism of drugs, including key molecules, pathways or modules.

**3.3**

**Material basis**

The chemical components and their related properties of modern medicine or natural medicine, including the name, type, physical and chemical properties, and pharmacokinetic parameters of these chemical substances, *etc.*

**3.4**

**Drug targets**

The biomolecules inside the body that can be affected by drugs, including Protein, RNA, and DNA, *etc.*

**3.5**

**Network analysis**

The deep analysis and mining of the biomolecular networks related to diseases or drug interventions, including basic network analysis (degree, betweenness, clustering coefficient and other basic network parameters) and deep network analysis (network modules and dynamic analysis, *etc.*).

**3.6**

**Biological functional annotation**

It refers to the annotation and enrichment of biological functions such as the Pathway and gene ontology (GO) in the disease-related biomolecular networks or those with drug interventions using bioinformatics methods.

**3.7**

**Biological functional prediction**

Based on the regularity results of network analysis, biological functions are predicted with bioinformatics and artificial intelligence, *etc.*

## 4 Evaluation requirements

The requirements of network pharmacology evaluation include two types—those of the general evaluation and the scalability evaluation.

a) The general evaluation requirements: It should include the basic evaluation contents necessary for network pharmacology analysis, which is the basic requirement to ensure the authenticity of the analysis results.

b) The scalability evaluation requirements: It requires to carry out deep evaluation analysis on the basis of a) for the different analysis objects (diseases and drugs) and analysis purposes (such as database development, algorithm development, mechanism study, diagnosis and treatment discovery and drug development), as shown in Table 1.

**Table 1 Evaluation requirements**

| Evaluation contents | | Disease-targeted analysis | | | | Drug-targeted analysis | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Database development | Algorithm development | Mechanism study | Diagnosis and treatment discovery | Database development | Algorithm development | Mechanism study | Diagnosis and treatment discovery |
| Reliability | Data source | ● | ● | ● | ● | ● | ● | ● | ● |
| | Data information | ● | ● | ● | ● | ● | ● | ● | ● |
| | Correlation information | ● | ● | ● | ● | ● | ● | ● | ● |
| | Software | ○ | ● | ○ | ○ | ○ | ● | ○ | ○ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | algorithm | | | | | | | | |
| | Analysis method | ● | ● | ● | ● | ● | ● | ● | ● |
| | Verification method[1] | - | ● | ● | ● | - | ● | ● | ● |
| | Model building[2] | - | ○ | ● | ○ | - | ○ | ● | ○ |
| Standardization | Information extraction | ● | - | - | - | ● | - | - | - |
| | Information conversion | ● | - | ○ | ○ | ● | - | ○ | ○ |
| | Algorithm implementation | - | ● | - | - | - | ● | - | - |
| | Analysis pathway | - | ● | ● | ● | - | ● | ● | ● |
| | Verification process | - | ● | ● | ● | - | ● | ● | ● |
| Rationality | Data screening | - | - | - | - | - | - | ● | ● |
| | Analysis indicator | - | ● | ● | ● | - | ● | ● | ● |
| | Verification model[2] | - | ○ | ● | ○ | - | ○ | ● | ○ |
| | Detection indicator | - | ● | ● | ● | - | ● | ● | ● |

Note: "●" refers to general evaluation contents, while "○" refers to the scalability evaluation contents. "-" means there are no requirements.

Note 1: The verification methods mainly include clinical and experimental ones.

Note 2: The model building and the "model" in the verification model mainly refer to animal models, cell models and others.

## 5. Evaluation process

The network pharmacology evaluation process includes data collection, network analysis and result verification. For each, the evaluation is specifically conducted from three main aspects: reliability, standardization and rationality (Table 2).

**Table 2 Evaluation process**

| Evaluation contents | Evaluation process | | |
|---|---|---|---|
| | Data collection | Network analysis | Result verification |
| Reliability | Data source<br>Data information[1]<br>Correlation information[2] | Software algorithm<br>Analysis method | Verification method<br>Model building |
| Standardization | Information extraction<br>Information conversion | Algorithm implementation<br>Analysis pathway | Verification process |
| Rationality | Data provenance<br>Data screening | Analysis indicator | Verification model<br>Detection indicator |
| Note 1: Data information includes diseases, disease targets, drugs, drug components, and component targets, *etc.*<br>Note 2: Correlation information includes protein interactions, gene-protein relationships, protein-metabolite interactions, and metabolite reaction process, *etc.* | | | |

## 6. Evaluation contents

### 6.1 Evaluation on reliability

It refers to whether the access to main data and their correlation information in the network pharmacology analysis, design of software algorithm and analysis method, and selection and model building of verification method are reliable and meet the analysis requirements. In general, the process of network pharmacology analysis can be divided into data collection, network analysis and result verification, and corresponding reliability evaluation is carried out for different processes. For reliability evaluation elements and indicators, please see Table A.1.

#### 6.1.1 Data collection

The reliability of the data source and collection method for drug material basis, biological targets and other basic data should be evaluated. The data collection includes literature search, software prediction, database retrieval, and experimental data analysis, *etc.*

Data verified by rigorous experiments or from authoritative literature are preferred to use. For those from software prediction and databases with non-literature sources, their reliability evaluation should be provided as much as possible, and those with high reliability are recommended.

### 6.1.2 Network analysis

In biological target network analysis, the reliability of new developed algorithm or the correctness and stability of the selected analysis method should be evaluated.

The evaluation indicators commonly used for new developed algorithm include the implementation of algorithms, the correctness of algorithm function, and the algorithm performance, e.g. accuracy, recall rate and F-score, *etc*.

When applying mature analytical methods in related fields to network pharmacology analysis, standard data set or experimental data are recommended for reliability analysis. The former shall consult data collection when evaluating their reliability.

For the case where the network analysis method has been used for research, the source of the analysis method should be clearly marked.

### 6.1.3 Result verification

The reliability and repeatability of the methods adopted should be mainly evaluated to ensure the credibility of verification results and final conclusions. The evaluation objects include, but are not limited to, the selections of the evaluation method (such as computer simulation, in vivo and in vitro experiments, and clinical trials), evaluation model (such as protein crystal structure, cell model, and animal model), and endpoint indicator (such as golden indicator and representative indicator). In vivo and in vitro experiments or clinical trials are preferred for verification.

## 6.2 Evaluation on standardization

The processes, such as data information extraction and conversion, software/algorithm development, network construction and analysis, and the experimental verification should be evaluated. Standardization evaluation ensures the accuracy and reproducibility of analysis results. For the standardization evaluation elements and indicators, please see Table A.2.

### 6.2.1 Data collection

The completeness and traceability of data information in the process of data collection, the clarity of data extraction and the standardization of data processing should be evaluated.

### 6.2.2 Network analysis

The definiteness of the evaluation process, the standardization of the evaluation method and the traceability of the analysis methods should be evaluated.

### 6.2.3 Result verification

The standardization of operational procedures and results analysis should be evaluated.

## 6.3 Evaluation on rationality

The rationality of data screening and filtering, network analysis index selection and threshold value determination, validation model and test index selection should be evaluated. For rationality evaluation elements and indicators, please see Table A.3.

### 6.3.1 Data collection

The rationality of key words selection and data screening principles should be evaluated in the process of data collection.

For the screening of pharmacodynamic components, analysis object, absorption pathway, effective part, markedly effective component, metabolic form, bioavailability and druggability and other factors affecting pharmacodynamic behaviors should be fully considered. Parameters affecting pharmacodynamic behaviors should be selected for the screening of pharmacodynamic components.

For the screening of targets and their interactions, data credibility and acquisition method rationality should be particularly investigated.

### 6.3.2 Network analysis

The rationality of network analysis indicators used to screen important targets (clusters), key pharmacodynamic components (clusters) and other factors should be evaluated. Relevant indexes of network analysis include: the

characteristics of nodes and edges (such as node degree, node centrality, and edge weight), network cohesion (such as density, clustering coefficient, subgraph, and connectivity), network separability (such as hierarchical clustering, and spectrum segmentation), network modularity, network motifs, etc.

For the specific diseases studied, the above indicators should be comprehensively considered in order to establish a reasonable disease-syndrome biomolecular network and determine appropriate network targets.

If a new computing method is applied in determining the pharmacodynamic component clusters and network targets, the importance of the selected pharmacodynamic components and network targets to the overall network stability shall also be investigated.

### 6.3.3 Result verification

The clinical trials, model representativeness and applicability, and relevance between testing indicators and network analysis results should be evaluated.

For the newly developed analysis algorithms of network pharmacology, it shall provide suitable performance evaluation indicators according to the result type, and verify the prediction results. Standard data sets can be applied for verification if necessary.

# Annex A

## (Informative)

## Evaluation elements and indicators

### A.1 The elements and indicators for reliability evaluation

For reliability evaluation elements and indicators, please see Table A.1.

Table A.1 Elements and indicators for reliability evaluation

| Evaluation process | Evaluation elements | Evaluation indicators |
|---|---|---|
| Data collection | Data accuracy | Accuracy and precision |
| | Data integrity | Recall ratio |
| | Data accessibility | Whether accessible to the public |
| Network analysis | Algorithm correctness | Correctness of arithmetic function and algorithm implementation |
| | Algorithm accuracy | Accuracy, specificity, sensitivity, recall rate and F-score |
| | Analysis stability | Root-mean-square error and mean absolute error |
| Result verification | Method reliability | Reliability[1] and validity[1] |
| | Result repeatability | Consistent rate |
| Note 1: Reliability and validity are mainly applicable to the reliability evaluation of verifications through clinical study, and animal or cell models. | | |

### A.2 The elements and indicators for standardization evaluation

For standardization evaluation elements and indicators, please see Table A.2.

**Table A.2 Elements and indicators for standardization evaluation**

| Evaluation process | Evaluation elements | Evaluation indicators |
|---|---|---|
| Data collection | Completeness of data description | Whether the key information of the data is clearly described |
| | Data traceability | Whether the relevant data can be traced based on the description information |
| | Clarity of data extraction | Whether the keyword is accurately described<br>Whether the extraction rule and method are clear |
| | Standardization of data processing | Whether the conversion and docking methods of data from different sources are clearly described |
| Network analysis | Clarity of the analysis process | Whether the algorithm design or network analysis processes are clearly described |
| | Standardization of evaluation method | Whether algorithm development undergoes rigorous methodological evaluation |
| | Traceability of analysis method | Whether the applied analysis methods or technical indicators can be traced to the source |

| | | |
|---|---|---|
| Result verification | Standardization of operating procedure | Whether the model applied is clear<br>Whether the operation procedure is clearly described |
| | Standardization of result analysis | Whether the evaluation indicators of results are clear<br>Whether the description of results is objective and accurate |

## A.3 The elements and indicators for rationality evaluation

For rationality evaluation elements and indicators, please see Table A.3.

**Table A.3 Elements and indicators for rationality evaluation**

| Evaluation process | Evaluation elements | Evaluation indicators |
|---|---|---|
| Data collection | Rationality of information extraction | Whether the search keywords selected are consistent with the research objective;<br>Whether the search keywords are complete |
| | Rationality of information screening | Whether the data screening principles meet the relevant requirements of the research content;<br>Whether the screening indicators selected meet the screening requirements |
| Network analysis | Applicability of analysis method | Whether the network analysis method adopted is consistent with the research objective |
| | Rationality of analysis indicator | Whether the analysis indicators selected meet the needs of network analysis |
| Result verification | Model applicability | Whether the model adopted is relevant to the research objective and whether it is representative |
| | Rationality of evaluation indicator | Whether the evaluation indicator meets the requirements of research objective |

## Annex B

## (Informative)

## Specifications for writing a research report

### B.1 Title and abstract

Both the title and abstract shall indicate the research object. In the abstract, it shall also briefly describe the research objective, method, result, and conclusion and significance of the network pharmacology analysis.

### B.2 Foreword

It shall elaborately elucidate the research background, principles and other contents. As to the specific research objective, it shall provide exact clinical efficacy or experimental evidence as much as possible, such as the high-quality RCT study, cohort study, real-world research result, or reliable research data.

### B.3 Methods and results

#### B 3.1 Research design

An overview of key contents in the research design shall be reported, such as the research object, method and type (such as dry experiment, and combination of dry and wet experiments), and data source (the way of obtaining data). A research flow chart shall be provided when necessary.

#### B 3.2 Research object

B 3.2.1 For disease-related research, it shall provide the standard name of the disease, and if necessary, the current version of ICD disease code number. The studies on a traditional Chinese medicine (TCM) syndrome shall correctly write its name which shall meet the relevant requirements of the *National Standard for Clinical Diagnosis and Treatment Terminology of Traditional Chinese Medicine (syndrome part)*.

B 3.2.2 For drug-related research, it shall provide the standard names of compounds or the unique identified information of the compounds, and if necessary, their structural formulas. As to the compound formula of Chinese herbs, the source and composition of the formula, as well as the standard names

of every Chinese herb it includes shall be provided. Latin or English names are recommended for Chinese herbs.

**B 3.3 Data source**

B 3.3.1 It shall describe the data source as elaborately as possible, such as the literature data, database retrieval or experimental data. As to the ways of obtaining data, all repeatable detailed parameters shall be provided, and the description of data source limitation if necessary.

B 3.3.2 For data obtained by database retrieval, it shall provide the database name, source, version, and retrieval data and strategy, as well as the database references for web database. The descriptive statistics such as the access address and data collection shall also be provided if necessary.

For data obtained from literature, it shall provide the original references and describe the way of obtaining these reference data. If necessary, descriptive statistics shall be carried out on the literature data.

For data obtained from experiments, it shall provide specific experimental methods, objects (related to this research) and conditions, as well as the way of obtaining experimental results. If necessary, the methodological verification results of the experimental methods shall also be provided.

**B 3.4 Network analysis**

B 3.4.1 It shall elaborately describe the relevant elements and their interactions in network construction, and the methods and indicators of network analysis. The biological significance shall be provided in the network analysis result. In the network construction, it shall describe the relationship between the relevant elements of network and the overall data. For a filtered subset, it shall reflect its rationality and provide specific screening methods, basis and principles, as well as elucidate its relationship with the research objective.

B 3.4.2 The network analysis method shall specifically describe the following:

-- Analysis content and indicators, such as the basic parameters of network (the characteristics of nodes and edges, the cohesive characteristics of the network,

and the modularity of the network), and their relationship with the research objective.

-- Network analysis strategy. If necessary, the pathway flow chart of the analysis shall be provided. For a non-original network analysis method, it shall provide the source of the method, its analysis parameters, references, and name and version of the analysis software. If necessary, the sensitivity analysis results shall also be provided for the analysis algorithm with parameter selection.

-- For the original analysis algorithm, it shall describe the principles, specific implementation steps, implementation methods, parameter settings, and programming language of the new algorithm. If a standard data set is used, it shall provide its reliability analysis result. If necessary, the results of comparison with the popular algorithms and the robustness analysis shall also be provided.

-- The network analysis results shall have clear biological significance. If there is a biological function annotation, it shall provide the type of the annotation (such as GO, Pathway, and Disease) and elaborately describe the method, parameters, software name and version of the annotation, as well as their relationship with the research objective.

**B 3.5 Result verification**

**B 3.5.1** It shall describe the verification method, strategy and its relationship with the research objective in detail. The verification with combined multiple methods is recommended. For non-original method, it is not recommended to verify it only with a computer-aided way or literature data.

**B 3.5.2** What shall be provided for result verification:

-- For computer-aided verification, it shall provide the name, reason, source, reference, parameter setting, software name and version, and comparison analysis result of the algorithm; While for literature data verification, it shall provide the basis, literature source, and retrieval data, as well as describe the ways of obtaining data from the original literature and their reliability analysis result.

-- For experimental research verification, it shall elaborately describe the experimental objects, materials, models and methods, as well as the sample collection and processing method, detection indicators, data acquisition method and analysis result. Its relationship with the research objective shall also be clarified.

-- For clinical research verification, it shall elaborately describe the research design and objects, inclusion and exclusion criteria, informed consent, trial implementation process, data management, sample collection strategy and method, sample processing method, detection indicators and statistical analysis result, and clarify the relationship with the research objective. If necessary, the approval documents by the ethics committee shall be provided.

**B 3.5.3** For studies focusing on developing network pharmacology algorithm, database, and computational analysis platform, it is necessary to make reasonable verification on the prediction analysis results obtained by the algorithm, database and the platform.

-- According to the type of prediction result, the analysis performance indicators and reliability evaluation indicators are provided, and the consistency evaluation result for standard data set if necessary.

-- The result reliability is verified by rigorous clinical trials or experimental studies. Among them, the reliability verification based on clinic and experiment has a high level of evidence.

**B.4 Discussion**

The overall result explanation shall be given prudently according to the research objective. On this basis, the methodological research shall increase the analysis on the generalizability of the methodology, while the applied research shall increase the analysis on the interpretability of research result. In addition, the limitations of research result shall be analyzed, including the source of uncertainty, and any potential factors that may affect the research result.

**B.5 Other contents**

In addition to the above contents, it shall also make clear whether the original data is accessible in the research report, and if necessary, provide the access to it. As to the analysis method, it shall provide the software packages used in the research and their version numbers, and if necessary, the analysis algorithm source code. For other original data, methods, analysis results, and other supplementary information not mentioned in the article, the access to the supplementary information shall be provided.