The 2015 WHO EML as a global standard:

an innovative approach or just an opportunity for new and effective medicines?

3rd International PPRI Conference,
Vienna – 13 October 2015

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World Health Organization

Essential Medicines

Guiding principle: A limited range of carefully selected essential medicines leads to better health care, better medicines management, and lower costs

Definition: Essential medicines are those that satisfy the priority health care needs of the population

World Health Organization

EML criteria (EB 109/8, 2001)

- Disease burden and public health need/relevance
- Sound and adequate data on the efficacy (on relevant outcomes), safety and comparative cost-effectiveness
  - "Absolute cost of the treatment will not constitute a reason to exclude a medicine from the Model List that otherwise meets the stated selected criteria"
  - "*Affordability changed from a precondition into a consequence of the selection*" (Hogerzeil, BMJ, 2004)
- WHO (good) management and oversight of CoIs
- Other considerations: regulatory status (off-label), availability, guidelines

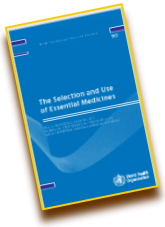
A quotation

- In 1977, the World Health Organization (WHO) published the first Model List of Essential Medicines (Essential Medicines List, EML). The EML assisted health authorities in selecting products for primary health care.
- It introduced the idea that some medicines are more important than others.
- Many later considered the first EML 'a revolution in public health'.

't Hoen EFM., et al
A quiet revolution in global public health:
The World Health Organization's Prequalification of Medicines Programme
Journal of Public Health Policy, 2014

World Health Organization

… 38 years of EML



1977 1st Model list published, **208** active substances

- List revised every two years by WHO Expert Committee

- 2002 Revised procedures approved by WHO (EB109/8, 2001)

2015 EML update (April 2015): 416 medicines

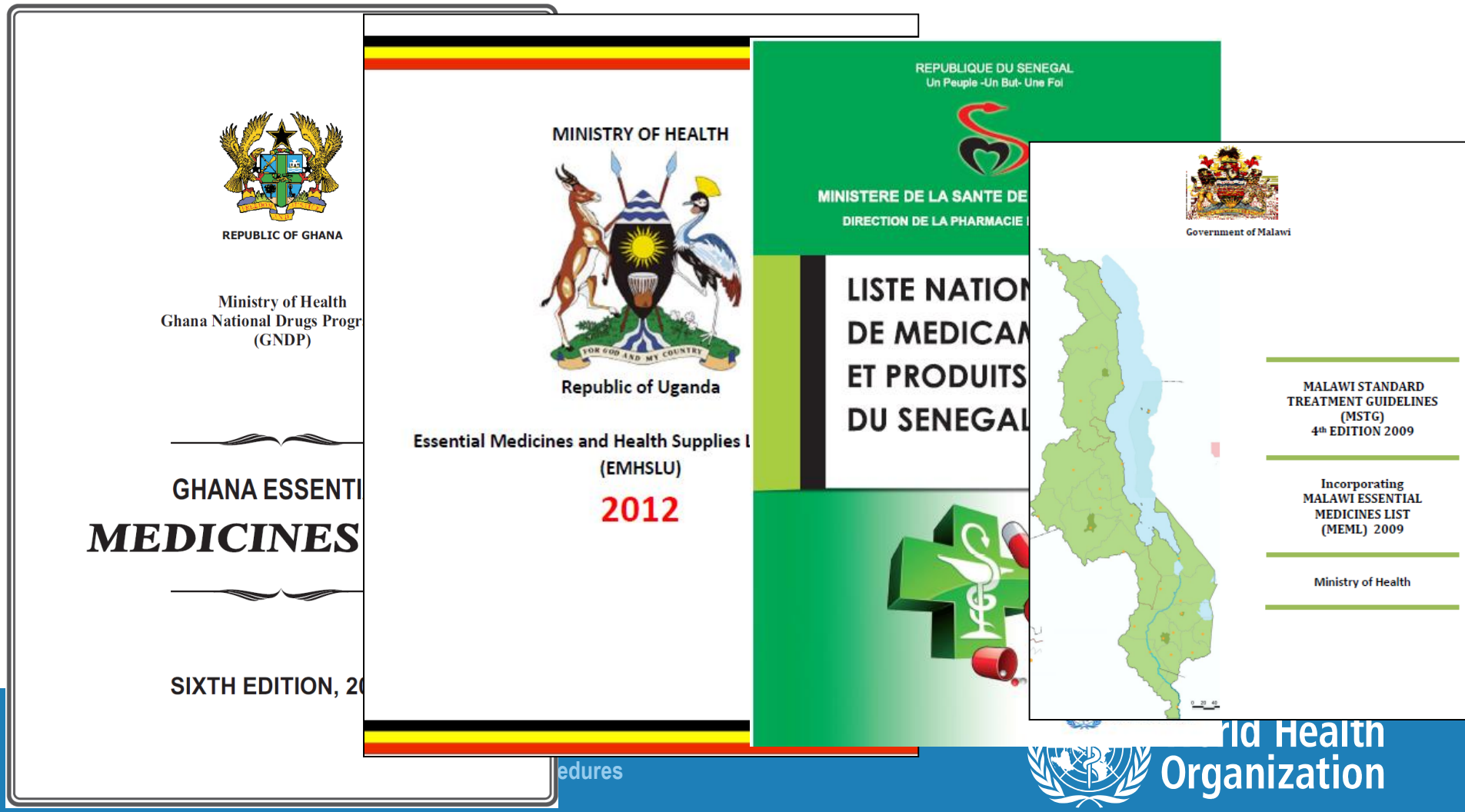
- **EML Adult: 416 medicines**
- Core List: 293
  - FDC's on core list: 26
- Complementary list: 114

- **EMLc Children: 289 medicines**
- Core list: 207
  - FDC's on core list: 11
- Complementary list: 76

World Health Organization

What is EML useful for … as a Model List

- National EMLs & reimbursement agencies/decisions



WHO 2015 update

Cancer medicines, HepC, TB and some rejections

Somehow a repositioning?

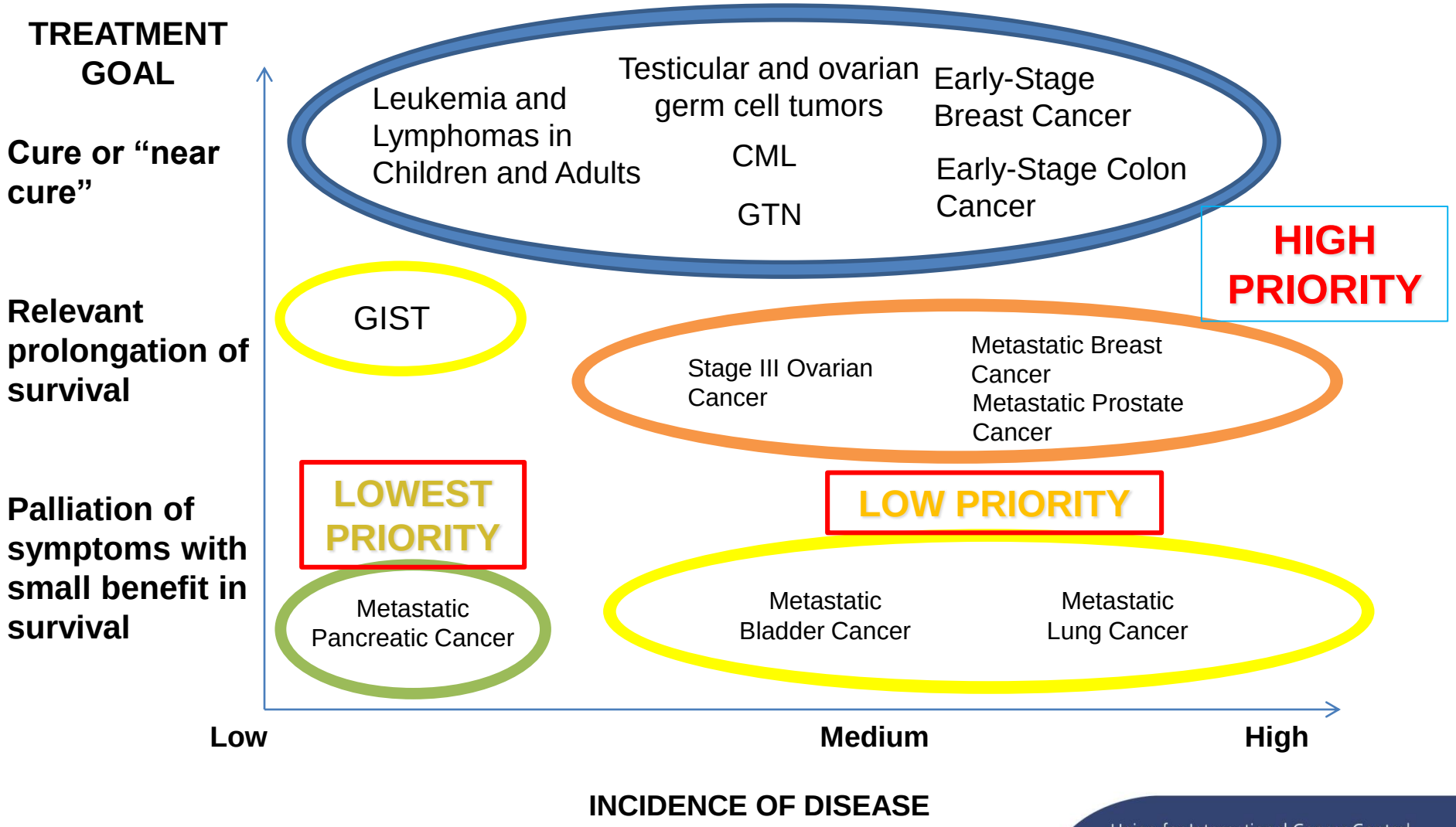
EML 2015:
77 applications and a few big challenges

- Cancer drugs: a large comprehensive review was commissioned (29 applications)
- New highly effective HCV drugs (new direct antiviral, single agents and combinations, IFN free regimens)
- MDR-TB drugs (4) and 1 for TB prophylaxis
- Rejections: New oral anticoagulants (NOACs), polypill, ranibizumab

WHO EML 2015:
Comprehensive Cancer updates

A very selective approach

Methodology to Develop Proposal for Revisions



Slide credit: Dr. Gilberto Lopes

Diseases Addressed

ADULT CANCERS		PEDIATRIC CANCERS
AML and APL (adult+ped)	GTN	ALL
CLL	Head and neck cancer	Burkitt lymphoma
CML	Hodgkin lymphoma	Ewing sarcoma
DLBCL	Kaposi sarcoma	Hodgkin lymphoma
Early stage breast cancer	Metastatic breast cancer	Osteosarcoma
Early stage cervical cancer	Metastatic colorectal cancer	Retinoblastoma
Early stage colon cancer	Metastatic prostate cancer	Rabdomyosarcoma
Early stage rectal cancer	Nasopharyngeal cancer	Wilms tumor
Epithelial ovarian cancer	Non-small cell lung cancer	
Follicular lymphoma	Ovarian germ cell tumors (adult+ped.)	
GIST	Testicular germ cell tumors (adult+ped)	

EML cancer update template: large B cell lymphoma

- A highly effective regimen CHOP: 55% cure rates
- Adding rituximab: 70% cure rates (15% absolute benefit)

Substantial chance for cure with drugs alone in a moderate-incidence disease: Large B-cell lymphoma is a disease that is highly curable with drugs alone. Surgery offers no chance for cure (though biopsy is necessary to establish a diagnosis). Four old, relatively inexpensive drugs (cyclophosphamide, doxorubicin, vincristine, and prednisone, or CHOP) can cure approximately 55% of patients (i.e. the cure rate increases from 0% to 55% with CHOP alone). At the same time, the addition of the newer biologic agent rituximab, when added to CHOP, can increase the cure rate to about 70% (i.e. cure rate increases from 55% to 70% with addition of rituximab), but at substantial increase in cost and difficulty of administration (the R-CHOP regimen is about 30 times more expensive than CHOP).

UICC EML Costing Scenarios

DIFFUSE LARGE B-CELL LYMPHOMA

CHOP Scenario

A patient with a body surface area of 1.8m^2 receiving R-CHOP for 6 cycles.

Essential Regimen: CHOP: Chemotherapy only, 6 cycles

	Unit Size and Cost	Units required for entire regimen	Total Cost
Cyclophosphamide	$8.75 per 500mg vial $2.89 per 1g vial	6x 500mg vials + 6x 1g vials	$ 69.83
Doxorubicin	$6.48 per 50mg vial	12 vials	$ 77.75
Vincristine	$2.61 per 1g vial	18 vials	$ 47.02
Prednisone	$0.03 per 100mg tab-cap	30 tab-caps	$ 0.81
Total Cost			**$ 195.41**

UICC EML Costing Scenarios

"Back of the Envelope" Calculations

R-CHOP Scenario

A patient with a body surface area of 1.8m^2 receiving R-CHOP for 6 cycles.

Advanced Regimen: R-CHOP: Chemotherapy plus monoclonal antibody, 6 cycles

	Unit Size and Cost	# of units necessary for a full course of treatment	Total Cost
Rituximab	$14.65 per 10mg/ml ampoule	408 ampoules	$ 5,976.38
Cyclophosphamide	$8.75 per 500mg vial $2.89 per 1g vial	6 500mg vials + 6 1g vials	$ 69.83
Doxorubicin	$6.48 per 50mg vial	12 vials	$ 77.75
Vincristine	$2.61 per 1g vial	18 vials	$ 47.02
Prednisone	$0.03 per 100mg tab-cap	30 tab-caps	$ 0.81
Total Cost			**$ 6,171.79**

New EML cancer medicines main criterion: magnitude of absolute benefits

- **Imatinib**: vast majority of patients in remission at 7 yrs
- **Rituximab** (large B cell lymphomas): 15% absolute increase in survival rates (from 50-55% to 70%)
- **Trastuzumab**: early stage breast cancer: up to 13% increase in survival in high risk women (from 37% to 50% survival rates at 3-6 yrs)
- Same approach (using absolute efficacy estimates) applied to all proposed regimens

Cancer update 2015: a selective investment

green: additions, red: rejections, yellow: next EC

Breast cancer	Colorectal	Lung	Prostate	Haematology	Others
Trastuzumab Capecitabine Aromatase inhibitors (letrozole, anastrozole, examestane) Pertuzumab TDM1	Oxaliplatin Capecitabine Irinotecan	Gemcitabine Cisplatin Erlotinib Gefitinib	Hormonal (bicalutamide, goserelin, buserelin)	Imatinib, Nilotinib, Dasatinib Rituximab Bendamustine ATRA (APML) Arsenic trioxide	GCSF (granulcyte colony stimulating factors) DES

EML comprehensive cancer review: methodology

- The cancer WG and the WHO Expert Committee used magnitude of clinical benefits to select medicines and regimes though they did not endorse an explicit threshold
- **Some medicines included in EML are cost effective AND unaffordable**: this will require **new** actions to increase access
- Next step: hot to involve more the research community and the regulatory/reimbursment agencies in this discussion

WHO EML 2015
New Hepatitis C medicines (DAA)

An inclusive approach

EML 2015 - New HepC medicines

- The Committee recommended the addition of six oral direct-acting antiviral agents for hepatitis C, including

Sofosbuvir	**ledipasvir + sofosbuvir**
Simeprevir	**Daclatasvir**
ombitasvir + paritaprevir + ritonavir ± dasabuvir	

- The recommendations for inclusions were based on the comparative efficacy, increased tolerability and the potential public health impact
- The very high cost of hepatitis C medicines was considered and the Committee recommended WHO to take actions at global level to make these medicines more accessible and affordable.

EML evidence synthesis: a good example

WHO Essential Medicines List Application

OMBITASVIR, PARITAPREVIR/RITONAVIR co-formulated tablet with or without DASABUVIR

Application prepared by Andrew Hill, Liverpool, UK

How to present all available evidence: phase 3 trials

… how to be more comparative?

Table 5. Phase 3 clinical trials in genotype 1 infected patients with ombitasvir/paritaprevir/r and dasabuvir, with or without ribavirin (intent-to-treat analyses)

Study reference	Study design	Patient characteristics	Intervention	SVR12, n(%)	VF or relapse, n(%)	D/C due to AE, n(%)
SAPPHIRE-I (Feld et al. 2014)	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN (GT1a and GT1b), no cirrhosis (n=631)	3D + RBV 12wks (n=473)	GT1a: 307/322 (95.3%) GT1b: 148/151 (98.0%)	GT1a: 7/322 (2.2%) GT1b: 1/151 (0.7%)	3/473 (0.6%)
PEARL-III (Ferenci et al. 2014)	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN (GT1b), no cirrhosis (n=419)	3D + RBV 12wks (n=210)	209/210 (99.5%)	1/210 (0.5%)	0
			3D alone 12wks (n=209)	207/209 (99.0%)	0	0
PEARL-IV (Ferenci et al. 2014)	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN (GT1a), no cirrhosis (n=305)	3D + RBV 12wks (n=100)	97/100 (97.0%)	2/100 (2.0%)	0
			3D alone 12wks (n=205)	185/205 (90.2%)	16/205 (7.8%)	2/205 (1.0%)
TURQUOISE-II (Poordad et al. 2014)	Multicentre, randomised, open-label, Phase 3	TN & TE (GT1), cirrhotic (TN: n=160; TE: n=220)	3D + RBV 12wks (TN: n=86; TE: n=122)	TN: GT1a: 59/64 (92.2%) GT1b: 22/22 (100.0%) TE: GT1a: 65/76 (85.5%) GT1b: 45/46 (97.8%)	13/208 (6.2%)	4/208 (1.9%)
			3D + RBV 24wks (TN: n=74; TE: n=98)	TN: GT1a: 52/56 (92.9%) GT1b: 18/18 (100.0%) TE: GT1a: 62/65 (95.4%) GT1b: 33/33 (100.0%)	4/172 (2.3%)	4/172 (2.3%)
SAPPHIRE-II (Zeuzem et al. 2014)	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TE (GT1a and GT1b), no cirrhosis (n=394)	3D + RBV 12wks (n=297)	GT1a: 166/173 (96.0%) GT1b: 119/123 (96.7%)	GT1a: 5/173 (2.9%) GT1b: 2/123 (1.6%) All PT-relapse	3/297 (1.0%)
PEARL-II (Andreone et al. 2014)	Multicentre, open-label, Phase 3	TE (GT1b), no cirrhosis (n=179)	3D + RBV 12wks (n=88)	85/88 (96.6%)	0	2/88 (2.3%)
			3D alone 12wks (n=91)	91/91 (100.0%)	0	0

Abbreviations: TN. Treatment-navie; TE, treatment-experienced; GT, genotype; 3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin; VF, virologic failure; D/C, discontinued; AE, adverse events

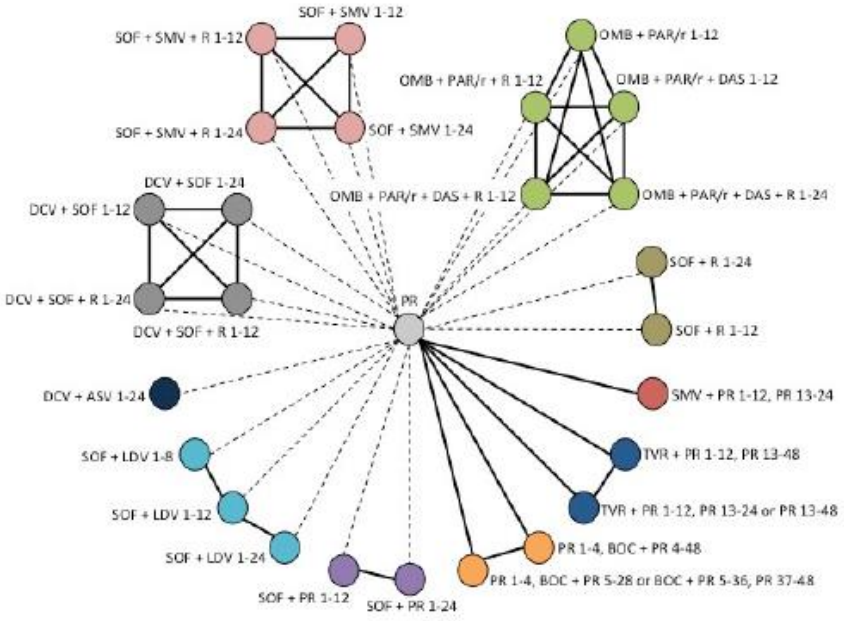
What evidence synthesis and overall appraisal do we really need?

GLOBAL EVALUATIVE

Table 3: Summary of comparative estimates of sustained virological response for treatment-naïve hepatitis C genotypes 1 and 4

Comparison	No. patients (No. arms)	Pooled proportion of SVR, % *(95% confidence interval)*	Difference in SVR, % *(95% confidence interval)*	Network meta-analysis, *relative risk (95% credible interval)*	Risk of Bias	Incon-sisten-cy	Indire-ness	Impre-cision	Magni-tude of effect	Public-ation Bias	GRADE
SMV + SOF vs.	40 (4)	97.32 (90.35, 100.00)									
PR	1564 (16)	46.86 (41.87, 51.86)	50.45 (								
TVR + PR	641 (7)	76.47 (70.21, 82.74)	20.84 (								
BOC + PR	901 (4)	66.43 (61.81, 71.05)	30.89 (								
SMV + PR	686 (5)	80.51 (77.54, 83.47)	16.81 (								
SOF + PR	464 (3)	90.18 (87.48, 92.89)	7.14 (-								
SOF + R	390 (9)	77.26 (67.98, 86.54)	20.06 (								
SOF + LDV	1028 (8)	97.65 (96.03, 99.26)	-0.33 (-								
DCV + SOF	195 (5)	98.35 (96.14, 100.00)	-1.03 (-								
DCV + ASV	265 (2)	83.07 (75.99, 90.15)	14.24 (								
OMB + PAR/r	1399 (8)	96.99 (95.19, 98.78)	0.33 (-								

Figure 2: Network diagram of the individual treatments informing comparative estimates for the treatment-naïve genotypes 1 and 4 population



Legend: Circles (nodes) represent individual treatments; the colours of the circles represent like treatments according to the groupings. Solid lines represent direct head-to-head comparisons; dashed lines represent simulated comparisons.

Important: ongoing trials

Important for the EC to have the "big picture" for its final recommendations, …

including the status of independent research and of head-to-head comparisons

Table 7. Ongoing trials of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin

Trial identifier	Location	Population	Geno-type	Treatment regimen (duration)	Expected completion
Phase 2					
CORAL-I (NCT01782495)	US, Australia, Europe	TN, liver or renal transplant recipient, with or without cirrhosis (on immunosuppressant regimen)	GT1	Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)	Mar 2017
NIAID (NCT02194998)	US, Puerto Rico	TN, with or without cirrhosis, with HIV-1 co-infection	GT1	Ombitasvir/paritaprevir/r + dasabuvir + RBV (12/24 weeks)	Jan 2016
Phase 3					
GIFT-I (NCT02023099)	Japan	TN/TE with or without compensated cirrhosis	GT1b	Ombitasvir/paritaprevir/r (12 weeks)	Oct 2015
GIFT-II (NCT02023112)	Japan	TN/TE with or without compensated cirrhosis	GT2	Ombitasvir/paritaprevir/r + RBV (12/16 weeks)	Sept 2015
QAQISH (NCT02247401)	Egypt	TN/TE, with or without cirrhosis	GT4	Ombitasvir/paritaprevir/r + RBV (12/24 weeks)	Aug 2016
TURQUOISE-III (NCT02219503)	US, Canada, Belgium	Compensated cirrhosis	GT1b	Ombitasvir/paritaprevir/r + dasabuvir (12 weeks)	Nov 2015
TURQUOISE-IV (NCT02216422)	Russia, Belarus	Compensated cirrhosis	GT1b	Ombitasvir/paritaprevir/r + dasabuvir + RBV (12 weeks)	Dec 2015
TURQUOISE-CPB (NCT02219477)	US, Canada, Germany	TN/TE with decompensated cirrhosis	GT1	Ombitasvir/paritaprevir/r + dasabuvir + RBV (12/24 weeks)	Oct 2016
RUBY-I (NCT02207088)	US	TN with renal impairment, with or without cirrhosis	GT1	Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)	Mar 2016
AGATE-I (NCT02265237)	US, Canada, Europe	TN/TE with compensated cirrhosis (inc. DAA experienced)	GT4	Ombitasvir/paritaprevir/r + RBV (12/16/24 weeks)	Jan 2017
TOPAZ-I (NCT02219490)	Canada, Europe, Israel	TN/TE, with or without cirrhosis; long-term outcomes	GT1	Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)	Dec 2020
TOPAZ-II (NCT02167945)	US	TN/TE, with or without cirrhosis; long-term outcomes	GT1	Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)	Mar 2020
MALACHITE-I (NCT01854697)	Canada, Europe, Australia, South America	TN, non-cirrhotic; randomised against telaprevir-based therapy	GT1	Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12weeks)	Jul 2015
MALACHITE-II (NCT01854528)	South America, Europe	TE; randomised against telaprevir-based therapy	GT1	Ombitasvir/paritaprevir/r + dasabuvir + RBV (12 weeks)	Jul 2015
Follow-up (NCT01773070)	US, Canada, Europe, Australia, NZ, Puerto Rico,	Follow-up study of prior AbbVie Phase 2/3 studies	Mainly GT1	Follow-up only	Oct 2016

EML 2015: what's specific about HepC drugs?

- "Inclusion on the EML of **all DAAs** proposed in the applications aims at
  - **promoting competition** among available alternatives and
  - **allowing for the selection of optimal combination treatment regimens**, which may or may not be existing fixed-dose combinations."

- Given the challenges of using existing diagnostic tests, highly effective, pan-genotypic treatment strategies should become the focus of a global approach **and a priority for independent research, with clinical trials directly comparing various DAA combinations**.

- The Committee also recommended that WHO continue to work on existing approaches to managing prices and evaluate alternative strategies to improve affordability and access

EML 2015: some rejections

- Polypill for secondary CV prevention *(lack of meaningful benefits, not clear if we were recommending a product or a concept and what were the combinations and the recommended doses)*
- NOACs *(marginal benefits over warfarin, lack of antidote, doubts on monitoring)*
- Ranibizumab intravitreal for age-related macular degeneration and diabetic macular edema *(substantial overlapping with bevacizumab and risk of reducing access to the inexpensive off label bevacizumab)*

EML 2015 update: implications

- The Expert Committee recommended an engagement with all stakeholders to discuss thresholds for a relevant clinical benefit and for cost-effectiveness
- Existing policy options do not seem to be sufficient to ensure global access to Essential Medicines
- The approach adopted by the Expert Committee was the application of existing criteria together with important considerations in order to facilitate access to essential medicines